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Broken Heart Strings - Psychological Stress in Cardiac Patients after Chordae Tendineae Rupture

Inauguraldissertation
zur Erlangung des Doctor scientiarum humanarum (Dr. sc. hum.)
an der
Medizinischen Fakultät Heidelberg
der
Ruprecht-Karls-Universität

vorgelegt von
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aus
Plymouth, Großbritannien
2019

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Acronyms

6MWT the Six-Minute Walk Test

AC Anna Cranz

ACS acute coronary syndrome

AHA American Heart Association

AMI acute mitral insufficiency

AMR acute mitral regurgitation

ARIC Atherosclerosis Risk in Communities

ASD acute stress disorder

CAD coronary artery disease

CAPS Clinician-Administered PTSD Scale for DSM-5

CBT Cognitive Behavioural Therapy

CDI-PTSD Cardiac-disease-induced post-traumatic stress disorder

CHD coronary heart disease

CHF congestive heart failure

CI confidence interval

CMR cardiac magnetic resonance

CN Christoph Nikendei

CPR cardiopulmonary resuscitation

CT Chordae tendineae

CTR Chordae tendineae rupture

CVD cardiovascular disease

DEP depression

DES Dissociative Experiences Scale

DSM Diagnostic and Statistical Manual of Mental Disorders

DSM-V Diagnostic and Statistical Manual of Mental Disorders fifth edition

ECG electrocardiogram

ENRICHD Enhanced Recovery in Coronary Heart Disease Patients

EROA effective regurgitant orifice area

FDS Questionnaire for Dissociative Symptoms

FS Fractional Shortening

GAD General anxiety disorder

HERS Heart and Estrogen Replacement Study

HF heart failure

HR Hazard ratio

HRQoL health-related-quality of life

IABP intra aortic balloon pump

LA left atrium

LVEDD left ventricular end-diastolic diameter

LVEF left ventricular ejection fraction

LVH left ventricular hypertrophy

LV left ventricular

MD mean

MEDAD medication adherence

MI myocardial infarction

MR mitral regurgitation

MV mitral valve

NSTEMI non-ST-segment elevation myocardial infarction

NYHA New York Heart Association classifications

PCI percutaneous coronary intervention

PD panic Disorder

PDS Post-traumatic Diagnostic Scale

PHQ Patient Health Questionnaire

PM papillary muscle

PTSD Post-traumatic stress disorder

PTSS Post-traumatic stress symptoms

QoL Quality of life

RF regurgitation fraction

RR Risk ratio

RVol regurgitation volume

SD standard deviation

SES socio-economic status

SNRI serotonin-norepinephrine reuptake inhibtor

SSRI serotonin reuptake inhibitors

STEMI ST-segment elevation myocardial infarction

TA thematic analysis

TCA tricyclic antidepressants

TTE transthoracic echocardiography

VIF Variance inflation factor

VIF variance inflation factors

WHO World Health Organisation

Part I

Dissertation

'The tackle of my heart is crack'd and burn'd, And all the shrouds wherewith my life should sail Are turned to one thread, one little hair: My heart hath one poor string to stay it by...'

William Shakespeare's King John (5.7.52-5)

Chapter 1

Introduction

The heart has held a key role in understanding the human body since antiquity (Singer, 1958). In the fourth century B. C., the Greek philosopher and physician Aristotle (384-322 BC) believed it to be the supreme organ of the human body (Van Praagh & Van Praagh, 1983). Throughout the ages, the heart has been seen as the seat of intelligence, motion, and sensation(Findlen & Bence, 1999). In the second century, Galen of Pergamon (129-216 AD), another Greek physician, carefully observed many of its unusual physical properties in his treatise 'On the Usefulness of the Parts of the Body' (May, 1968). He wrote that '[...]the heart is a hard flesh, not easily injured. In hardness, tension, general strength, and resistance to injury, the fibres of the heart far surpass all others, for no other instrument performs such continuous, hard work as the heart' (Findlen & Bence, 1999). In Galen's conception, the heart's fibres and strings expanded or contracted likewise under the experience of strong emotion (May, 1968). In the sixteenth and seventeenth centuries, advances in anatomy enabled a sharper conception of the true functioning of the heart (Reynolds, 2007). An English physician, William Harvey (1578-1657 AD), is thought to be the first to describe the heart's chief role in the body's blood circulatory system in his book, 'On the Circulation of the Blood' (Khan, Daya & Gowda, 2005). As a result, the idea of the heart as key organ function executor ceased (Reynolds, 2007). Nevertheless, Harvey still referred to the heart as the 'king' or the 'sun' of the body (Findlen & Bence, 1999). Across the ages, the heart has remained an inherent symbol of the soul and human emotions (Reichbart, 1981). In his works, Shakespeare refers to Galen's fibres as symbols for emotion. Here, they become 'heartstrings', or 'threads' that can 'crack' under stress or be 'pulled' under emotional upheaval (Findlen & Bence, 1999). Through

Shakespeare's visual vocabulary, the above-cited passage from his play 'King John' gives us a sense of the heart's importance: strong emotion may cause the heart to enlarge to such an extent that the fine strings become the quintessential threads that hold it together and prevent it from breaking (Iyengar, 2014, p. 349). Beyond the emotional and semantic implications of broken heart strings for literature and culture, chordae tendineae rupture CTR is a life-threatening event, often resulting in acute mitral regurgitation acute mitral regurgitation (AMR) with significant haemodynamic dysfunctions that require immediate medical intervention. While the psycho-emotional comorbidities of heart disease have received much attention, so far little is known about patients' psychological burden after AMR due to CTR. This work aims to elucidate the background of psychological stress in cardiac patients. By using a mixed-method approach, we will assess and discuss cardiac patients' psychological burden after AMR due to CTR. Furthermore, case sample data will be compared to age and sex-matched control sample of patients which have suffered myocardial infarction (MI).

Following this introduction (Chapter One), the reader will be given a brief introduction to cardiovascular disease in general, and acute mitral valve insufficiency and chordae tendineae rupture in particular (Chapter Two). Also, the reader will receive an overview of the current state of research with regard to psychological stress and cardiovascular disease (Chapter Three). After presenting the aims and hypothesis of this work's study (Chapter Four), a detailed report of the materials and methods used for its implementation is given (Chapter Five). Then, we will report on our quantitative and qualitative results (Chapter Six), before discussing them against the backdrop of the extent findings of the field (Chapter Seven). Finally, this work's study is critically scrutinised with regards to its limitations and possible further research and a conclusion is given (Chapter Eight). In Chapter Nine, this work is summarised first in English, then in German language. Additional information, such as study instruments and consent forms can be found in the Appendix.

Chapter 2

Background

This chapter aims to briefly introduce the reader to the prevalence, diagnosis, and treatment, as well as mortality and prognosis of selected cardiac diseases that form the backdrop of this work. Particular focus is put on the nature and context of chordae tendineae rupture.

2.1 Cardiovascular disease

cardiovascular disease (CVD) is the leading cause of death in the world, accounting for 31% of all deaths in 2013 (Clark, 2013). Figure 2.1 shows a world map of the global distribution of CVD mortality rates in males (age standardised, per 100,000) as published by the World Health Organisation (WHO) in collaboration with the World Heart Federation and World Stroke Organisation in 2011 as part of the Global Atlas On Cardiovascular Disease Prevention and Control. The report states that recent decreases in cardiovascular disease mortality have plateaued in the United States (Bhave & Eagle, 2017; Wilmot, O'Flaherty, Capewell, Ford & Vaccarino, 2015; Micha et al., 2017) and worldwide death rates due to CVD are on the increase, rising 42% between 1990 and 2013 (Roth et al., 2015). In 2015, there were an estimated 422,7 million cases of CVD (Roth et al., 2017).

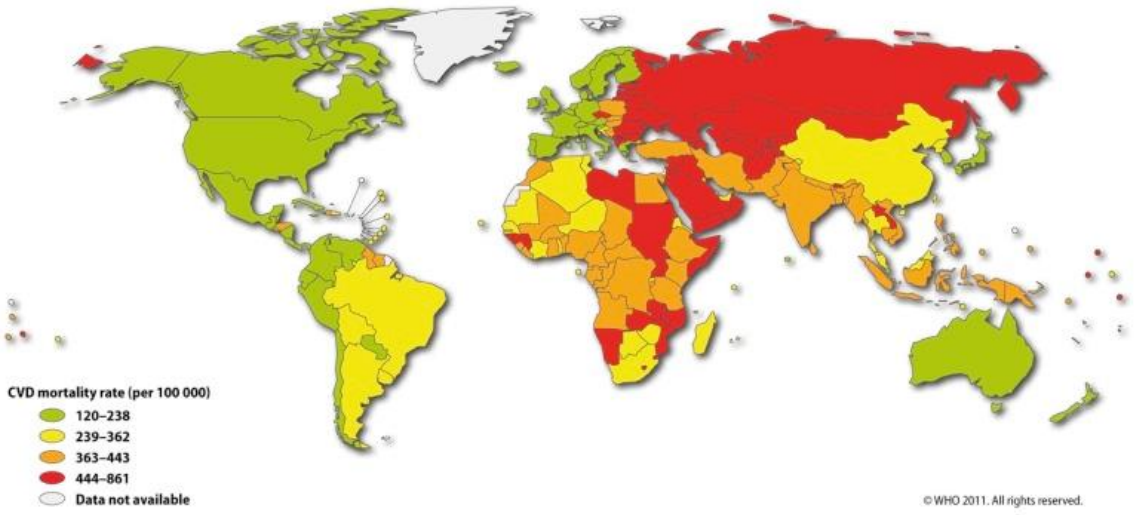

Figure 2.1: Global mortality rates in males due to cardiovascular disease per 100.000 in 2011[a]

[a] Source:(Mendis, Puska & Norrving, 2011) Originally published jointly by the World Health Organisation in collaboration with the World Heart Federation and World Stroke Organisation in 2011 as part of the Global Atlas On Cardiovascular Disease Prevention and Control; permission for use granted by World Health Organisation, Mai, 29th, 2019 (Permission ID: 289666).

The percentage of premature deaths from CVDs ranges from 4% in high-income countries to 42% in low-income countries, leading to growing inequalities in the occurrence and outcome of CVDs between countries and populations (Roth et al., 2017).

2.1.1 Coronary heart disease

In their 2016 review on the epidemiology of coronary heart disease and acute coronary syndrome (Sanchis-Gomar, Perez-Quilis, Leischik & Lucia, 2016), Sanchis-Gomar et al. summarise the incidence, prevalence, trend in mortality, and general prognosis of coronary heart disease coronary heart diseases (CHDs) and related conditions. They specify that the umbrella term cardiovascular disease CVDs describes diseases of the heart and blood vessels and comprises, among other conditions, coronary heart disease CHDs and coronary artery disease coronary artery diseases (CADs) as well as acute coronary syndrome acute coronary syndromes (ACSs) (Mendis et al., 2011). Sanchis-Gomar et al. highlight, that although the terms CAD and ACS as well as CHD are frequently used interchangeably, they are not the same. They define ACS as a subcategory of CAD, whilst CHD is a result of CAD (Sanchis-Gomar et al., 2016). Moreover, CAD is characterised by atherosclerosis in coronary arteries and can be asymptomatic, while ACS is commonly symptomatic. Here, symptoms often include unstable angina, which is frequently associated with myocardial infarction MIs (see Section 'Myocardial infraction'), re-

gardless of the presence of CAD (Lippi, Sanchis-Gomar & Cervellin, 2016). In turn, CHD mortality results from CAD. As Sanchis-Gomer et al. point out, the development of novel immunoassays in the measurement of cardiac troponins has prompted a revision of this classification (Sanchis-Gomar et al., 2016). Today, the spectrum of clinical conditions previously defined as 'unstable angina' has been progressively reclassified as either non-myocardial infarction or myocardial infarction (Cervellin, Mattiuzzi, Bovo & Lippi, 2016). To improve legibility, this work will refer to CAD as CHD.

Prevalence, mortality, and prognosis

In an Heart Disease and Stroke Statistics update in 2016, the American Heart Association (AHA) reported that 15.5 million persons older than 20 years of age in the USA have CHD (Mozaffarian et al., 2016). For both sexes, data show that prevalence increases with age and, shockingly, one American will suffer an myocardial infarction approximately every 42 seconds. Since the 1990, absolute numbers of CVD deaths have significantly increased (Sanchis-Gomar et al., 2016). However, largely due to a shift in age demographics and causes of death worldwide, the age-standardised death rate has fallen by 22% over the same period of time (GBD, 2013).

When writing about the epidemiology of cardiovascular disease, the Framingham Heart Study cannot go unmentioned (W. B. Kannel, Dannenberg & Abbott, 1985). It is a long-term, ongoing cardiovascular cohort study of residents of the city of Framingham, Massachusetts that initially began in 1948 with 5,209 adult participants, currently assessing the third generation of participants (Mahmood, Levy, Vasan & Wang, 2014; Dawber, Meadors & Moore Jr, 1951). Data from 44 years of follow-up of this cohort and 20 years of follow-up of their offspring has enabled the approximation of the incidence of initial coronary events, such as myocardial infarction, angina pectoris, unstable angina, and sudden and non-sudden coronary deaths (Gordon, Kannel, Hjortland & McNAMARA, 1978; Lerner & Kannel, 1986; W. Kannel, 1987). The Framingham data shows that for people aged 40 years, the lifetime risk of developing CHD was 49% in men and 32% in women, while the lifetime risk was 35% in men and 24% in women for those aged 70 years. The incidence for total coronary events strongly increased with age (Sanchis-Gomar et al., 2016). For women, incidence was generally 10 years later than for men. However, the incidence sex ratio decreased progressively with advancing age or the more serious manifestations of CHD, such as myocardial infarction and sudden death (Lloyd-Jones et al., 2010). Moreover, compared to people aged 35–64 years, the incidence at ages 65–94 years more than doubled in men and tripled in women.

Furthermore, coronary events made up 33% to 65% of atherosclerotic cardiovascular events in men and 28% to 58% in women. In addition, angina pectoris was commonly more frequent in men than women. For women aged over 75 years, angina pectoris was more frequent than myocardial infarction and was more likely to be uncomplicated (80%). For men, angina often occurred after myocardial infarction (66%). Across all ages, myocardial infarction was most dominant in men in whom only 20% of events were preceded by long-standing angina; the percentage was even lower for silent or unrecognised myocardial infarction (Lerner & Kannel, 1986; W. B. Kannel, Cupples & D'Agostino, 1987). However, whether the initial presentation of CHD is an acute myocardial infarction or stable angina is not only conditioned by sex: a case-control study assessing first CHD presentation adults with either myocardial infarction ($n = 916$) or stable exertional angina ($n = 468$) found that recent prior therapy with statins and beta blockers affects the clinical presentation (Go et al., 2006).

2.1.2 Myocardial infarction

An acute myocardial infarction is defined as a myocardial necrosis caused by an acute obstruction of a coronary artery. Symptoms generally include chest discomfort with or without dyspnea, nausea, and sweating or cold sweating. The diagnosis commonly results from the electrocardiogram (ECG) and the presence or absence of serological markers. myocardial infarction treatment comprises platelet aggregation inhibitors, anticoagulants, nitrates, beta-blockers, statins, and reperfusion therapy. In ST-segment elevation myocardial infarction ST-segment elevation myocardial infarction (STEMI), emergency reperfusion is performed using fibrinolytics, percutaneous coronary intervention (PCI), or occasionally coronary bypass surgery. In myocardial infarction without ST-segment elevation non-ST-segment elevation myocardial infarction (NSTEMI), reperfusion is performed by percutaneous intervention or coronary bypass surgery (Thygesen et al., 2012).

Prevalence, mortality, and prognosis

In the USA, about 1.5 million people suffer a myocardial infarction every year (Thygesen et al., 2012). This has a fatal outcome for $400,000 - 500,000$ people. In Germany, the incidence is about 300 infarctions per $100,000$. The epidemiology of myocardial infarction has been assessed by several studies with regard to the influence of sex, race, and age. The Atherosclerosis Risk in Communities (ARIC) study focused on the risk of CHD events among $360,000$ residents aged $35 - 74$ years in four communities in the USA (Watkins et al., 2005; Rosamond et al., 2008).

Between 1987 and 1996, they assessed a total of 14.942 hospitalised patients with definite or probable myocardial infarction. The age-adjusted incidence of hospitalised myocardial infarction was highest in black men and lowest among white women (Thygesen et al., 2012). However, case-fatality rates after myocardial infarction decreased significantly during the 1987–1996 period in both genders, i.e., by -6.1% and -6.2%. These improvements in CHD outcome were attributed to secondary rather than primary prevention strategies (Watkins et al., 2005; Rosamond et al., 2008; Goldberg, Yarzebski, Lessard & Gore, 1999). NSTEMI in relation to STEMI have increased over the past years(Furman et al., 2001; Rogers et al., 2008; Roger et al., 2010). A report from the National Registry of myocardial infarction reviewed over 2.5 million myocardial infarction cases between 1990 and 2006 (Rogers et al., 2008) and found that the proportion of myocardial infarction due to NSTEMI increased from 19% in 1994 to 59% in 2006. This change in proportion was associated with an absolute decrease in the incidence of STEMI and either a rise or no change in the rate of NSTEMI (Roger et al., 2010). The incidence of myocardial infarction decreased significantly after 2000 and the incidence of STEMI decreased markedly after 1999 within a large community-based population (Yeh & Go, 2010). The authors attributed reductions in short-term case fatality rates for myocardial infarction to a decrease in the incidence of STEMI, a lower rate of death after NSTEMI (Yeh & Go, 2010), and the enhanced diagnostic effectiveness of modern cardiac troponin immunoassays in the detection of minor myocardial injury.

Risk factors

Although many cases of myocardial infarction seemingly occur suddenly, patients frequently have an ominous coronary risk profile (Sanchis-Gomar et al., 2016) and signs of pre-symptomatic CHD. Approximately $2-4\%$ of the general population has silent coronary ischemia, which despite being an asymptomatic condition, can be easily detected with an exercise test or ambulatory ECG monitoring. The prevalence is significantly higher in men with two or more major coronary risk factors (10%) and in patients with known CHD ($25-50\%$ in stable angina patients, for instance) as diagnosed via exercise testing or ambulatory monitoring (W. B. Kannel, 1985). The most specific indicator of the existence of silent myocardial ischemia in ECG recordings is a Q-wave myocardial infarction (Sheifer, Manolio & Gersh, 2001). Framingham Heart Study data suggests that for patients who had suffered a renewed myocardial infarction during routine biennial ECG, the infarct was silent in 26% of men and 34% of women (W. B. Kannel, Cupples & Gagnon, 1990). In men, the frequency of unrecognised myocardial infarction was

higher in diabetic than in non-diabetic individuals (39% *vs*. 18%) (W. B. Kannel, 1985). For the past decades, it has been shown that the risk for CHD death and all-cause mortality has substantially decreased after Q-wave myocardial infarction, largely attributed to improvements in post-myocardial infarction therapies and in post-myocardial infarction survival of individuals with depressed left ventricular (LV) systolic function (Guidry et al., 1999). Nevertheless, silent myocardial infarction as well as clinically apparent myocardial infarction are strongly associated with age (Goldberg, Glatfelter, Burbank-Schmidt, Lessard & Gore, 2006; Sigurdsson, Thorgeirsson, Sigvaldason & Sigfusson, 1995). Although the coronary risk factor profiles of individuals with previously unrecognised myocardial infarction are similar to those of patients with clinically recognised myocardial infarction (Sheifer et al., 2001), two CVD risk factors, namely hypertension and diabetes mellitus, are associated with a higher likelihood of having unrecognised myocardial infarction. The Framingham Study confirmed diabetes as a risk factor for silent infarction in men but not in women (W. B. Kannel, 1985). In men with diabetes, the fraction of unrecognised myocardial infarction was more than twice as high as in those without (39% *vs*. 18%)(W. B. Kannel, 1985; Shlipak et al., 2001). However, in patients over 75 years with test-positive angina, the coronary mortality ratio has been shown to be higher in women (LaCroix et al., 1990). The incidence/prevalence of myocardial infarction increases progressively in women after the age of 45 (Maddox et al., 2008). Women are generally $6-10$ years older than men during their first symptomatic myocardial infarction and also more likely to have a history of diabetes, hypertension, hyperlipidemia, heart failure, and unstable angina patterns (White et al., 1993; Maynard, Litwin, Martin & Weaver, 1992). The outcomes in women with ACS and no ST elevation [unstable angina or NSTEMI has received particular attention: despite showing more comorbidities, women have a similar (Hochman et al., 1997) or even better outcome than men (Chang et al., 2003; Hochman et al., 1999; Roger et al., 2000). According to a multivariate analysis (Roger et al., 2000), women showed a trend toward a lower risk of death (*Riskratio*(RR), 0.81) and a significantly reduced risk for a cardiac event (RR, 0.83).

2.1.3 Heart failure

myocardial infarction is the most common cause of heart failure (HF) worldwide and for almost 50 years HF has been recognised as a determinant of adverse prognosis after myocardial infarction (Cahill & Kharbanda, 2017). HF is defined as 'a clinical syndrome that occurs as the end result of any structural or func-

tional cardiac disorder that impairs the ability of the ventricles to fill with or eject blood'(Sidebotham & Doughty, 2007; Yancy et al., 2013). This has been translated into several validated diagnostic criteria (e.g., the Framingham criteria (McKee, Castelli, McNamara & Kannel, 1971) and the European Society of Cardiology criteria (Members et al., 2012)). However, the primary definition of HF as a clinical syndrome has led to differing clinical, imaging, and bio-marker definitions coexisting in clinical practice and research. Unlike myocardial infarction there is no 'universal definition' and consequently, the diagnosis of HF is often heterogeneous between studies and over time (Thygesen et al., 2012). HF following myocardial infarction has been assessed using clinical criteria, such as the Killip and New York Heart Association classifications (NYHA) (Killip III & Kimball, 1967; Yancy et al., 2013).

The NYHA stages

The NYHA classification system is a scale used to categorise heart failure into defined stages. As a result, the indicated treatment for a specific stage of heart failure can be applied. The following symptoms are used in order to classify a heart failure as enumerated below: shortness of breath (dyspnea), frequent nightly urination (nocturia), discoloration of the skin due to lack of oxygen saturation (cyanosis), general weakness and fatigue, angina pectoris or cold extremities, oedemas.

NYHA stage I Movement or performance is not impeded. Complete absence of symptoms or ailments under stress despite diagnosis of a cardiac disease.

NYHA stage II Slightly reduced resilience under pressure. No symptoms present while at rest or light stress. Increased stress leads to appearance of symptoms.

NYHA stage III Severe reduction of resilience under pressure. Symptoms already become present even with light increase of stress.

NYHA stage IV Symptoms are constantly present, even when at rest.

Diagnosis

The development of echocardiography led to objective measurement of ejection fraction and ventricular volumes as an intrinsic part of a HF diagnosis and thus redefined clinical HF scoring (Cahill & Kharbanda, 2017). The timing of HF following myocardial infarction is important clinically, mechanistically, and for research. Three key time periods need to be distinguished: HF at the index myocardial infarction presentation, during the course of the first admission, and after discharge. Notably, research studies often fail to define HF timing, making comparison between

studies challenging. Cahill et al. state that particularly older studies failed to treat HF as a time-dependent, progressive factor which is influenced by the up-front treatment, meaning that late-onset HF after myocardial infarction is less well characterised than HF at presentation (Cahill & Kharbanda, 2017). Several overlapping mechanisms contribute to HF after MI: HF during the index myocardial infarction occurs due to a combination of myocardial stunning, myocyte necrosis, decompensation of pre-existing HF or acute mitral regurgitation due to papillary muscle dysfunction or CTR. HF during hospitalisation may also be due to any of the above, compounded by fluid or contrast overload, renal dysfunction, or complications such as ventricular septal defect or cardiac tamponade. Late HF reflects the consequences of cardiomyocyte death and scar formation occurring alongside ventricular remodelling.

Mortality and prognosis

O'Connor et al. state that neurologically intact survival to hospital discharge is the key outcome compared to the simple return of spontaneous circulation (O'Connor et al., 2010). Although survival rates vary significantly, they list the following factors as favourable for a positive outcome: witnessed arrest, quick and effective bystander-initiated cardiopulmonary resuscitation (CPR), in-hospital location (particularly a monitored unit), initial rhythm of VF or VT, early defibrillation (of VT or VF after initial chest compression), post-resuscitative care, including circulatory support and access to cardiac catheterisation. Furthermore, in adults, targeted temperature management (body temperature of 32 to 36° C) and avoidance of hyperthermia reduces mortality (Bernard et al., 2002; Nielsen et al., 2013). In favourable circumstances, about 40% of patients survive to hospital discharge. Overall, in-hospital arrest (VT/VF and asystole/PEA) survival is about 25%. However, if factors are largely unfavourable (e.g., patient in asystole after unwitnessed, out-of-hospital arrest), survival is, sadly, unlikely. Overall, reported survival after out-of-hospital arrest is about 10%. Moreover, only about 10% of all cardiac arrest survivors have good CNS function at hospital discharge.

Treatment

Unsurprisingly, rapid intervention is essential and the treatment of primary causes is a key factor. CPR is an organised, sequential response to cardiac arrest. Severe circulatory shock is identified when no treatable conditions are present but cardiac motion or pulses are detected by ECG and IV fluid (eg, 1 L 0.9% saline, whole blood, or a combination for blood loss) is given. If response to IV fluid

is inadequate, one or more vasopressor drugs (e.g., norepinephrine, epinephrine, dopamine, vasopressin) are given. However, it remains controversial whether these benefit the outcome. In addition to primary cause treatment, post-resuscitative care typically includes the optimisation of oxygen delivery, rapid coronary angiography in patients with suspected cardiac aetiology, and targeted temperature management (32 to 36C $^{\circ}$ in adults) (Moler et al., 2017, 2015).

2.1.4 Blood flow through the heart

Before detailing the function of the mitral valve, it is important to bring to mind the general flow of blood through the heart, especially with regard to the symptoms CTR patients experience during AMR.

In brief, the heart pumps blood to all parts of the body. Blood has the function of providing oxygen and nutrients to the our organism and removing carbon dioxide and wastes. As blood flows through the body, oxygen store is used up, and the blood becomes low in oxygen(Klocke, 1976).

- Oxygen-poor blood returns to the heart through the superior vena cava and inferior vena cava.
- Low oxygen blood enters the right atrium, or the right upper chamber of the heart. From there, the blood flows through the tricuspid valve into the right ventricle, or the right lower chamber of the heart.
- The right ventricle pumps oxygen-poor blood through the pulmonary valve into the main pulmonary artery. From there, the blood flows through the right and left pulmonary arteries into the lungs.
- In the lungs, our blood is enriched with oxygen and carbon dioxide dissipated.
- The now oxygen-rich blood flows back into the left atrium, or the left upper chamber of the heart, through four pulmonary veins.
- Oxygen-rich blood then flows through the mitral valve into the left ventricle, or the left lower chamber.
- The left ventricle then pumps the oxygen-rich blood through the aortic valve into the aorta, the main artery that takes oxygen-rich blood out to the rest of the body.

2.1.5 The mitral valve

As this structure is central to this work, a very brief overview of the workings of the mitral valve will be given, before detailing the implications of acute mitral valve insufficiency following CTR.

The mitral valve functions as a valve between the left atrium and left ventricle, allowing blood to flow only from the atrium to the ventricle and not vice versa. It was named after its shape, which resembles that of the bishop's cap, also known as the mitre. The valve leaflets form two sails which are attached to Chordae tendineae (CT) or chordal tendons. These in turn are attached to a small muscle (papillary muscle) protruding into the ventricle (see Figure 2.2). This attachment prevents the valve leaflets from penetrating into the atrium when the chamber fills with blood and ejects into the aorta. In the healthy state, the edges of the two leaflets lie against each other, so that for this phase of heart action the atrium is completely separated from the ventricle. If the heart valve does not close properly, i.e. a leak develops, this is referred to as mitral valve insufficiency. If, on the other hand, it is not able to open completely when blood is pumped from the atrium into the chamber, this is called mitral stenosis (Baumgartner et al., 2017).

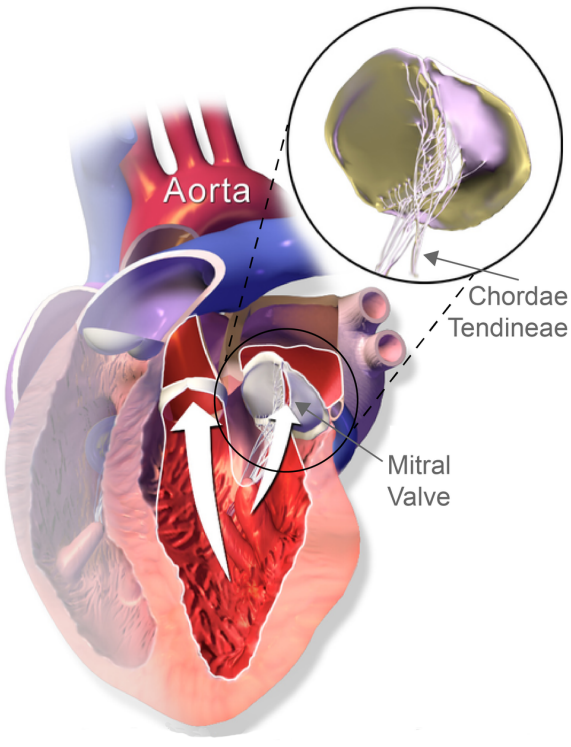

Figure 2.2: A schematic view of the mitral valve and an enlarged view of the mitral chordae tendineae. The white arrows indicate regurgitant blood flow.(staff & staff, 2014) [a]

[a] Source: Blausen.com staff (2014),'Medical gallery of Blausen Medical 2014'. WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436. This file is licensed under the Creative Commons Attribution-Share Alike 4.0 International license.

Prevalence and development

Mitral valve stenosis is the most common acquired heart valve defect worldwide (Baumgartner et al., 2017). In Germany, (and other industrialised countries), however, the frequency of their occurrence has significantly decreased in recent years compared to acquired aortic valve stenoses and mitral valve insufficiencies. In rare cases, a mitral valve stenosis can be congenital. Usually, it is caused by rheumatic fever several years before the heart valve disease was diagnosed. This is a consequence of a purulent streptococcal infection, which often manifests itself in the patient as tonsillitis, pharyngitis, or inflammation of the upper respiratory tract. A few weeks after infection, characteristic symptoms, such as inflammation of the inner lining of the heart or heart muscle (endocarditis, myocarditis), acute inflammation of the large joints, rheumatic nodules, etc., occur. In the context of this rheumatic fever, the mitral valve can thicken and calcify, resulting in narrow spots (stenoses). For some time now, streptococcus-induced inflammations 'streptococcal angina' have been promptly treated with antibiotics in Western industrial countries, so that rheumatic fevers with heart involvement are rare. As a result, mitral valve insufficiencies are more common today as mentioned above. These can also develop in the context of a rheumatic fever, which, as just described, is rather rare nowadays. However, the most common cause today is CTR papillary muscle dysfunction, which is a frequent complication following heart failure or CHD. Furthermore, leaks can also be caused by bacterial infections of the mitral valve (bacterial endocarditis). In addition to congenital diseases of the connective tissue that cause laxity, the mitral valve of the heart can also be damaged by drug abuse and heavy alcohol consumption.

Symptoms

If the mitral valve leaks, the blood flows back into the atrium and pulmonary veins during the filling and ejection phase of the ventricle, increasing the blood pressure in the pulmonary circulation due to the increased blood volume. The right heart has to fight against increased resistance and build more muscle, thus, reaching a critical point. When the body is weak (e.g. cold, ill, elderly etc.), the heart can no longer build up the necessary strength and fluid is squeezed out of the lungs and body, causing shortness of breath, general weakness, and oedema, such as water in the legs (Maleki, Alizadehasl & Haghjoo, 2017). In addition, tachycardia and cardiac arrest may become noticeable in the patient. In cases of a rupture of the papillary muscle or of several CT with flail of the mitral valve leaflet, the left heart cannot adapt to the sudden changes in pressure, which result in acute heart

failure. This event shall be treated in more detail in the following sections 'Acute mitral insufficiency' and 'Chordae tendineae rupture'.

The symptoms of a decompensated heart failure in mitral valve stenosis are similar (S. N. Shah & Sharma, 2019). The increased pressure that the left atrium would have to exert in order to press the blood into the chamber is not equal to this. It expands as more and more blood is added from the pulmonary circulation but less can be released into the ventricle. This distension is often the cause of a cardiac arrhythmia, called atrial fibrillation, which patients usually perceive as a general weakness during exertion and palpitations.

Diagnosis and therapy

Patient diagnosed with the above-mentioned symptoms are examined using echocardiography (ultrasound of the heart) and chest X-ray to determine and classify a disease of the heart valves and any other changes to the heart caused by it (Michaux, Skarvan, Filipovic & Seeberger, 2006). If a heart valve operation is necessary, a cardiac catheter examination is performed to determine the degree of severity and possible damage to the heart more precisely, or to determine a possible parallel coronary stenosis. Via the catheter, contrast medium is injected into the interesting vascular parts and heart sections and made visible under a mobile X-ray device. On the basis of the ECG and transthoracic echocardiography transthoracic echocardiography (TTE) findings, as well as in consideration of relevant risk factors, such as age and present comorbidities, a decision regarding valve repair or valve replacement is made (S. N. Shah & Sharma, 2019).

2.1.6 Acute mitral valve insufficiency

AMR is a potentially life-threatening cardiac emergency (Dudczak et al., 2016). It is characterised by sudden onset, rapid progression of pulmonary oedema, hypotension, and clinical signs of a left-sided heart failure which may finally result in a severe cardiac shock and, in some cases, pulmonary hypertension which may lead to acute right-sided heart failure (Barber, Ratliff, Cosgrove, Griffin & Vesely, 2001; Grande-Allen et al., 2001). AMR is often caused by the abrupt rupture of the valve's constraining structures and must be distinguished from chronic mitral regurgitation (MR) as the haemodynamic changes are far more dramatic in AMR. The sudden rupture of a single leaflet's chordae tendineae may cause the leaflet to 'flop backward' during systole (flail leaflet) resulting in severe valve incompetence. Hence, AMR can be rapidly fatal if mitral valve repair is not promptly performed (Depace, Nestico & Morganroth, 1985).

Diagnosis

Significant causes of AMR are chordae tendineae rupture, IE with the disruption of the MV leaflets or chordal rupture, ischemic dysfunction, or rarely the rupture of a papillary muscle, as well as malfunction of a prosthetic valve (Maleki et al., 2017). TTE is the gold standard for diagnosing and quantifying the severity of ischemic mitral valve insufficiency. In the acute setting, TTE is also the only method that is actually used and provides essential information about changes in valve size and ventricular geometry, thus allowing the causes and underlying mechanisms to be identified (Nickenig et al., 2013; Vahanian et al., 2012; Skarvan & Bernet, 2006). Insufficiency quantification is performed by determining jet length, jet width, and jet area in the colour Doppler, by evaluating the CW Doppler spectrum, by analysing pulmonary vein flow with pulsed Doppler, and by analysing proximal flow acceleration (effective regurgitant orifice area (EROA))(Michaux et al., 2006). Quantitative echocardiographic parameters used are the width of the Vena contracta, the regurgitation flow rate, the effective regurgitation area, the regurgitation volume (RVol), the regurgitation fraction (RF), the duration of regurgitation and the flow pattern in the pulmonary veins (Skarvan & Bernet, 2006).

Because the 'v' wave is significantly elevated in these patients, the reverse pressure gradient between the LV and left atrium (LA) drops at the end of systole, and the murmur can be decrescendo rather than holosystolic, ending well before the A2. It typically is lower pitched and softer than the murmur of chronic MR. A left-sided S4 commonly is found. Common PAH might increase the intensity of P2, and the murmurs of PI and TR also may be heard together with a right-sided S4. In patients with severe acute MR, a late systolic pressure rise (a v wave) may rarely cause the premature closure of pulmonary valve, an early P2, and the paradoxical splitting of S2 (Maleki et al., 2017).

acute mitral regurgitation, even if severe, frequently does not rise the whole cardiac size, as is seen on chest radiography, and might produce only mild LA enlargement despite a marked rise in LA pressure.

Echocardiography may display little increase in the internal diameter of the LA or LV, but augmented systolic motion of the LV is noticeable. The main findings on Doppler echocardiography are the severe jet of MR and the increase in the pulmonary artery pressure (Lancellotti et al., 2010).

Chronic regurgitation increases left atrial size and compliance, and, accordingly, left atrial pressures will be normal despite the regurgitant volume (Stout & Verrier, 2009). Conversely, acute mitral regurgitation increases volume into a normally compliant left atrium, resulting in a marked increase in left atrial pressure. A significant V wave may be evident in either condition, although it is more pronounced

in acute regurgitation. Because of the increased left atrial pressure from acute mitral regurgitation, pulmonary oedema is a common consequence. Preexisting conditions may affect tolerance of acutely increased left atrial and left ventricular volume. Patients with a history of chronic mitral regurgitation and preserved ventricular function may tolerate the marked increase in volume better, whereas patients with impaired ventricular function may quickly decompensate with acute worsening of mitral regurgitation. Those patients with pulmonary oedema associated with ST-segment elevation myocardial infarction often have coexistent mitral regurgitation, with under-appreciated severity and a poor prognosis (Fässler, 2014). As with acute aortic regurgitation, there is some degree of initial compensation afforded by an increased preload, but the inability of the ventricle and atrium to accommodate the increased volume results in marked increase in left ventricular end-diastolic and left atrial pressures (Lancellotti et al., 2010).

Prevalence, treatment, and mortality

The prevalence of mitral valve insufficiency is estimated to be $1-2\%$ in the total population and increases with age to over 10% for people aged 75 years and older (Nickenig et al., 2013; Vahanian et al., 2012). The classification is based on causes (ischemic - non-ischemic), mechanisms, and the progression over time. As patients in this state of emergency typically present acute pulmonary oedema or cardiogenic shock, the definitive treatment is immediate surgery after initial stabilisation through medical therapy, which includes nitrates, diuretics, and inotropic agents (Vahanian et al., 2012).

Afterload lessening is chiefly important in treating patients with acute severe MR. Intravenous nitroprusside may be lifesaving in patients with acute severe MR caused by the rupture of the head of a papillary muscle, complicating an AMR. It can stabilise clinical status, thereby permitting coronary arteriography and surgery to be performed with the patient in an ideal situation. In patients with acute severe MR who are hypotensive, an inotropic agent such as dobutamine must be administered with nitroprusside. Intraaortic balloon counterpulsation may be necessary to stabilise the patient while preparations for surgery are made (Maleki et al., 2017).

Emergency surgical management may be essential for patients with acute LV failure caused by acute severe MR. Emergency surgery is correlated with higher mortality rates than those for elective surgery for chronic MR. Nonetheless, unless patients with acute severe MR and HF are treated aggressively, a fatal outcome is nearly certain (Maleki et al., 2017). The pathogenesis of acute mitral regurgitation determines its management. In a series of acute mitral regurgitation (Stout & Verrier, 2009), there were several different causes: acute myocardial infarction (45%),

degenerative valvular disease (26%), and infective endocarditis (28%). Each of these causes is managed by different strategies, and each has different outcomes (Lorusso et al., 2008). Unlike aortic regurgitation, for which repair is rarely possible, mitral regurgitation may be treated with either repair or replacement. However, the risk of open heart surgery to repair or replace CT is often very high for unstable, mostly elderly patients (Adamo et al., 2017). Surgical mortality rates also are greater in patients with severe acute MR and refractory HF (NYHA functional class IV), than in those with prosthetic valve dysfunction, and those with active IE (of a native or prosthetic valve) (Maleki et al., 2017). Despite the higher surgical risks, the efficacy of early surgery has been established in patients with IE complicated by medically uncontrollable congestive HF and recurrent emboli.

Therefore, in this common scenario, AMR caused by chordal rupture is often treated with transcatheter mitral valve repair (Mokadam, Stout & Verrier, 2011), which is associated with lower operative mortality, preservation of left ventricular function, and better long-term survival when compared to open surgery (Hauptmannová et al., 2014)(Nishimura et al., 2014, 2017). Transcatheter mitral valve repair is a procedure that involves the approximation of the anterior and posterior mitral leaflets with the help of a suitable repair system (e.g. the MitraClip procedure), leading to the formation of a double-orifice valve (Feldman et al., 2011). The event of AMR is highly acute and associated with a poor prognosis (Barzilai, Davis, Stone, Jaffe & Groupab, 1990).

Data suggest that severe mitral regurgitation in patients with cardiogenic shock is not uncommon, approaching 7% of patients in the 'Should We Emergently Revascularize Occluded Coronaries in Cardiogenic Shock (SHOCK)' registry. The presence of acute mitral regurgitation in these patients is a very poor prognostic sign, with an observed mortality of 55%, improving to only 39% in patients selected for emergency surgery (Stout & Verrier, 2009). The SHOCK trial demonstrated that early revascularization improves outcomes at 6 months in patients with cardiogenic shock and acute myocardial infarction, and further analysis demonstrated the prognostic importance of mitral regurgitation in these patients (Thompson et al., 2000). Short- and long-term survival was inversely related to the degree of mitral regurgitation, arguing for more aggressive treatment of those patients with significant mitral regurgitation in the setting of acute infarction, with improved mortality in those patients undergoing early revascularisation (Picard et al., 2003). Thus, if surgical revascularisation is needed, the presence of severe mitral regurgitation should encourage rather than discourage surgical intervention.

In 5% of deaths from acute myocardial infarction, acute ischemic mitral valve insufficiency is the underlying cause (Reeder, 1995). Mortality during this early phase

of CTR treatment using transcatheteral approaches can reach up to 50% within the first 24 h, and up to 90% within 48 h following the occurrence. The peri-operative mortality, when using open surgery is also high $20 - 50\%$ (Enriquez-Sarano et al., 2005; Hickey, Wilcken, Wright & Warren, 1985; Seeburger et al., 2011). The cause of acute regurgitation also determines the outcome. This was demonstrated by a recent report of a series of patients undergoing surgery for acute severe mitral regurgitation that displayed an overall 30-day mortality of 22.5% with the best outcomes in those patients with degenerative disease (Lorusso et al., 2008).

Prognosis

The prognosis of acute mitral valve insufficiency is poor. Factors influencing the prognosis are age, comorbidities, clinical symptoms, previous treatments, degree of insufficiency, left ventricular pump function and diameter, left atrial size > 40-50 mm, pulmonary hypertension, atrial fibrillation, neurohumoral activation, and decreased oxygen uptake under stress (Enriquez-Sarano et al., 1999; Gillam & Schwartz, 2010; Nickenig et al., 2013; Valuckienė, Urbonaitė & Jurkevičius, 2015). The prognosis of mitral valve insufficiency after surviving myocardial infarction deteriorates significantly (36% mortality in development of mitral valve insufficiency in hospital admission vs. 16% mortality in development of mitral valve insufficiency during hospital admission) (Barzilai et al., 1990; Valuckienė et al., 2015).

2.1.7 Chordae tendineae

MV closure depends upon the correct functioning of each component of the valve apparatus, which comprises the annulus, the leaflets, and the CT (Khalighi et al., 2017). The CT are made of dense collagenous connective tissue which protrudes from the tip of the papillary muscle (PM) and adjoins to the MV leaflets. The MV chordae tendineae are shown in their tree-like structure in Figure 2.3. The PMs and CT form an integrated unit (the 'sub-valvular apparatus') providing the structural support for MV leaflets during ventricular contraction (Neely, Leacche, Byrne, Norman & Byrne, 2014). Commonly, pathological conditions connected with MV regurgitation are characterised by deviations of the sub-valvular apparatus from its healthy, homeostatic state (Ciarka & Van de Veire, 2011). Chordal rupture, which is a very common lesion in elderly patients (Gabbay & Yosefy, 2010), often leads to leaflet prolapse and blood leakage (Grenadier et al., 1985).

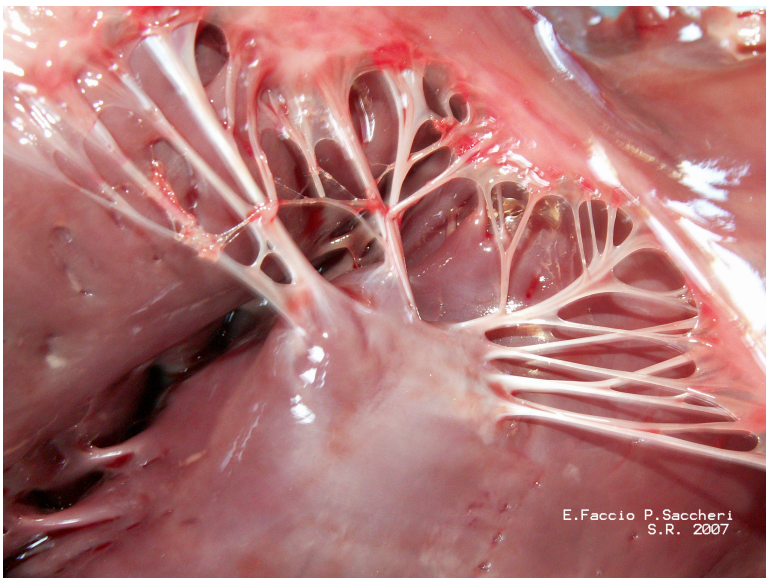

Figure 2.3: The MV chordae tendineae are made of dense collagenous connective tissue and form tree-like structures which protrude from the tip of the PM and adjoin to the MV leaflets[a]

[a] Source: E.Faccio & P.Saccheri. 2007. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.

The chordae tendineae have their origin by the tip of the papillary muscles and insert on the rough zone of the mitral leaflets (Degandt, Weber, Saber & Duran, 2007). After their origin and before their insertion, they split in numerous branches and interconnections that ensure a balanced distribution of the mechanical forces among chordae (Faletra et al., 2016). The simplest and perhaps most effective classification of chordae tendineae divides the chordae in three types: The first order chordae or marginal chordae insert on the free margins of leaflets. The rupture of these chordae always causes mitral regurgitation. The so-called commissural chordae are marginal chordae that insert on the free margin of commissures. The second order chordae or strut chordae insert on the confine between the rough and clear zones of the anterior leaflet. These chordae, usually two in number, are particularly robust and thick; the tension that they experience during the systole is in fact much higher than that of the first order chordae. Their function is other than that of impeding the eversion of leaflets. They actually reduce the motion of the lateral part of the anterior leaflet, leaving the central part much more mobile. Thus in systole the anterior leaflet takes a concave shape toward the outflow tract, and in diastole toward the inflow tract. This configuration facilitates the blood flowing into the aorta and into the LV, respectively. Moreover, these chordae appear to ensure a fibrous continuity between the leaflet and ventricular wall, supporting the contraction of longitudinal fibers of the LV. The third order chordae or basal chordae originate directly from the ventricular wall and insert only on the posterior leaflet. These chordae should limit the motion of the posterior leaflet. One

may speculate that the absence of basal chordae on the anterior leaflet should allow a greater mobility to the latter.

2.1.8 Chordae tendineae rupture

The rupture of the mitral chordae tendineae predominantly occurs in male adults older than 50 years of age (Gabbay & Yosefy, 2010). The severity of its clinical manifestation depends on the total number of ruptured chordae. Mild cases of CTR usually involve the disconnection of single chorda causing minimal haemodynamic constraints and requiring no treatment and usually remain asymptomatic. In contrast, patients who have suffered from significant rupture involving the acute simultaneous separation of multiple chords exhibit AMR as outlined above, which results in a medical emergency and requires immediate surgical intervention (Dolmatova et al., 2017).

As the condition is rare, only a handful of retrospective studies have described patient populations with CTR to date (Gabbay & Yosefy, 2010), with even fewer studies focusing on treatment modalities for these patients (Kazui & Kawazoe, 2004; Rankin et al., 2004). To describe national trends in the incidence and outcomes of patients with CTR, Dolmatova et al, (2016) conducted a study assessing patients diagnosed with CTR between 2000 and 2012 via the National (Nationwide) Inpatient Sample (NIS) registry (Dolmatova et al., 2017). They identified a total of 37,287 (14,833 mitral valve repair, 7780 mitral valve replacement) CTR cases. Their results suggest that overall, in-hospital mortality in CTR decreased by 3% from 2000 to 2012. From 2000 to 2012, the rate of mitral valve repair increased from 27.2% to 46.4% with a concurrent decrease in the rate of mitral valve replacement (from 27.8 to 17.7%). After multivariate adjustment, patient age ($OR = 1.04,\ 95\%\ CI = 1.03 - 1.06,\ P < 0.001$), congestive heart failure (CHF) ($OR = 2.08,\ 95\%\ CI = 1.19 - 3.64,\ P = 0.01$), myocardial infarction ($OR = 3.58,\ 95\%\ CI = 2.10 - 6.11,\ P < 0.001$), Deyo/Charlson comorbidity index ($OR = 1.23,\ 95\%\ CI = 1.07 - 1.41,\ P < 0.003$) and use of the intra aortic balloon pump (IABP) ($OR = 4.81,\ 95\%\ CI = 2.71 - 8.55,\ P < 0.001$) were found to be independently associated with greater odds of mortality in these patients (Dolmatova et al., 2017). Additionally, mitral valve replacement was significantly associated with higher costs of hospitalisation ($coefficient$ 15693, $95\%\ CI = 12638 - 18749,\ P < 0.001$). Increasing age and comorbidity index, history of CHF and myocardial infarction, and use of IABP were identified as factors that could increase the risk of mortality in patients with CTR. Overall, 1839 (4.9%) patients with CTR died during admission, including 284 (1.9%) of patients that

underwent mitral valve repair and 525 (6.8%) patients with mitral valve replacement. The mortality rate was highest among patients who did not receive any surgical intervention (7.2%, $P < 0.001$). Mortality was higher in patients who underwent mitral valve replacement when compared to patients that underwent repair (6.8% *vs*. 1.9%, $P < 0.001$). While no significant changes were observed in the incidence of CTR, or in the age or gender distribution of patients, a sustained increase in the severity of comorbidity index was observed. This may be a true increase that reflects the overall increase in prevalence of diabetes, cardiovascular disease, acquired immunodeficiency syndrome, and other chronic conditions (Vos et al., 2015; Leon & Maddox, 2015). On the other hand, it may be a consequence of improved diagnostic techniques, resulting in more accurate reporting of comorbidities in these patients. The increase in the burden of comorbidities could also be partly responsible for the significant increase in the costs of in-hospital care for both groups of patients undergoing MVR or MVP in our study (Sabaté, Sabaté & others, 2003). In addition, the trend of in-hospital mortality in patients with CTR decreased over time. This effect was observed in both groups of patients undergoing MVP and MVR. This could in part be explained by improvement in surgical techniques over time. Also, overall reduction in mortality might be due to increasing employment of MVP over MVR over the years (Gammie et al., 2009).

In the following, Chapter three aims to provide an overview of current research concerning cardiovascular disease and psychological comorbidity. First, general aspects will be discussed. The findings with regard to post-traumatic stress PTSD disorder will be reported, before current results with regard to depression and anxiety disorders are presented.

Chapter 3

Psychological stress and cardiovascular disease

The impact of psychosocial factors on cardiovascular diseases is increasingly recognised by patients, health care providers, and health care insurances. To date, as stated by the German Cardiac Society in its updated 2018 position paper(Albus et al., 2019), there is firm evidence supporting the relevance of psychosocial factors for coronary heart disease, chronic heart failure, arterial hypertension corroborating the need for their consideration in cardiological care. The following sections aim to provide a brief overview on the current state of knowledge on psychosocial factors and mental comorbidities often accompanying cardiovascular diseases. This chapter will cover aspects such as age, gender, socioeconomic status, and social support against the backdrop of a biopsychosocial model as well as introducing the concept of medication adherence.

3.1 General aspects and the biopsychosocial model

Commonly, onset and course of cardiovascular diseases can be described with the help of a biopsychosocial model: cardiovascular diseases develop before the backdrop of individual genetic dispositions and in interaction with interpersonal experiences over an individual's life span combined with environmental stressors resulting from complex socioeconomic and cultural milieu synergies (Albus, Ladwig & Herrmann-Lingen, 2014). It has been established that genetic risk factors play a lesser role than environmental and behavioural factors: individuals burdened by high genetic risk can reduce their risk to that of a person with low genetic risk through healthy life choices. The onset of cardiovascular diseases is closely tied to an unhealthy lifestyle (smoking, poor diet, inactivity, exposure to stress) and it

has been shown that premature deaths could be significantly reduced by actively addressing these risk factors (Albus et al., 2014).

3.1.1 Age

Although the risk for myocardial infarction increases with age, the actual risk is determined by modifiable risk factors (Dhingra & Vasan, 2012). Unsurprisingly, an older patient's risk factor profile will differ from that of a young heart attack patient. Although younger heart attack patients are often male and report familial genetic predisposition, their main risk factor for infraction is tobacco abuse (N. Shah, Kelly, Cox, Wong & Soon, 2016). Moreover, results of the INTERHEART study have shown that psychosocial risk factors, such as depression, critical life events, stress symptoms, and financial problems, account for 43.5% of the population's attributable risk in younger patients compared to 25.2% in older patients (Yusuf et al., 2004). Risk factors such as frailty, social isolation, and cognitive impairment seem to increase with age; for example, older chronic heart failure patients are more often in need of palliative care. The prevalence of atrial fibrillation increases continuously past the age of 50 (Kirchhof, 2016). In contrast, genetically conditioned and often life-threatening cardiac arrhythmias become manifest in the patient's thirties (Ponikowski et al., 2016).

3.1.2 Gender

In males, CHD prevalence is consistently higher and increases exponentially starting at the age of 45 (Gö\s swald, Schienkiewitz, Nowossadeck & Busch, 2013). CHD incidence generally increases when women reach the age of 55 years. However, they draw equal with males if they report low social status. Alabas et al. found that women were generally older and more likely to have comorbidities (but less likely to smoke) and show atypical symptoms at incidence, consequently often receiving sub-optimal guideline-based therapy (Alabas et al., 2017). This often leads to women seeking help only following longer latency. Consequently, women are less likely to receive state of the art therapy and in a timely manner. For CHF, it was shown that womens' reported symptoms of tiredness and exhaustion were often mistaken for signs of depression, while they were later diagnosed with CHF (Regitz-Zagrosek, Oertelt-Prigione, Seeland & Hetzer, 2010). This then often resulted in delayed treatment. As with acute coronary syndrome, arrhythmias such as paroxysmal supraventricular tachycardia, are more often misdiagnosed as panic attacks or attributed to other psychogenic symptoms in women than in men (Carnlöf, Iwarzon, Jensen-Urstad, Gadler & Insulander, 2017). Their results corroborate pre-

vious findings that women show worse relative survival and higher excess mortality than men (Alabas et al., 2017). Besides age, women show a higher prevalence of depression and post-traumatic stress disorder PTSD, which in turn is associated with higher cardiovascular risk (Vaccarino et al., 2013). Furthermore, McSweeney et al. (2016) were able to show that early stress experiences, low social status, and increased gender-specific role conventions in familial and professional environments were further risk factors for women (McSweeney et al., 2016). Moreover, higher stress vulnerability and stress exposure was associated with atypical cardiovascular pathologies in women, such as microvascular dysfunction or vasospasm (Vaccarino & Bremner, 2017).

3.1.3 Socioeconomic status

Defined via education, income, profession, and place of residence, socioeconomic status is a significant predictor of cardiovascular morbidity and mortality (Kamphuis, Turrell, Giskes, Mackenbach & van Lenthe, 2012). As mentioned before, cardiovascular diseases impact individuals with lower social status in high-income populations especially (Stringhini et al., 2017). Accordingly, it has been shown that if individuals retain a low social status, characterised by work-related factors (either no or precarious work contracts, unqualified work), environmental factors (low-grade housing, high crime rates, traffic noise, pollution), and high mental stress, throughout their life, this is associated with doubled cardiovascular mortality (Stringhini et al., 2017).

3.1.4 Social support

Lack of social support is associated with a higher risk of developing cardiovascular diseases and a higher risk of mortality (Stringhini et al., 2012). Moreover, for single men, lack of social support and loneliness are significant factors for overall and cardiovascular mortality (Stringhini et al., 2012). Xia et al. (2018) were able to show that the effect of loneliness on mortality is comparable to that of heavy smoking (15 cigarettes per day) (Xia & Li, 2018).

Early psychological stress exposure

Being exposed to psychological stress at a young age, such as violence, neglect, sexual and emotional abuse, as well as social discrimination, increases the risk for developing mental, cardiovascular, and metabolic illnesses, again leading to increased mortality (Juonala et al., 2016; Suglia et al., 2018). Furthermore, longitud-

inal studies have been able to show an inverse relationship between psychosocial well-being in childhood and adolescence on the one hand, and the incidence of atherosclerosis in adulthood on the other hand (Juonala et al., 2016).

3.1.5 Biopsychosocial mechanisms

As detailed previously, an elevated risk of cardiovascular morbidity and mortality is associated with psychosocial factors, such as low socioeconomic status, chronic stress, or mental comorbidity (Albus et al., 2014). Hence, drastically, the life expectancy of patients with severe mental disorders is generally decreased by up to 10 years compared to healthy populations. Figure 3.1 provides a summary of psychosocial risk factors for selected cardiovascular diseases (Gale, Batty, Osborn, Tynelius & Rasmussen, 2014; Wahlbeck, Westman, Nordentoft, Gissler & Laursen, 2011).

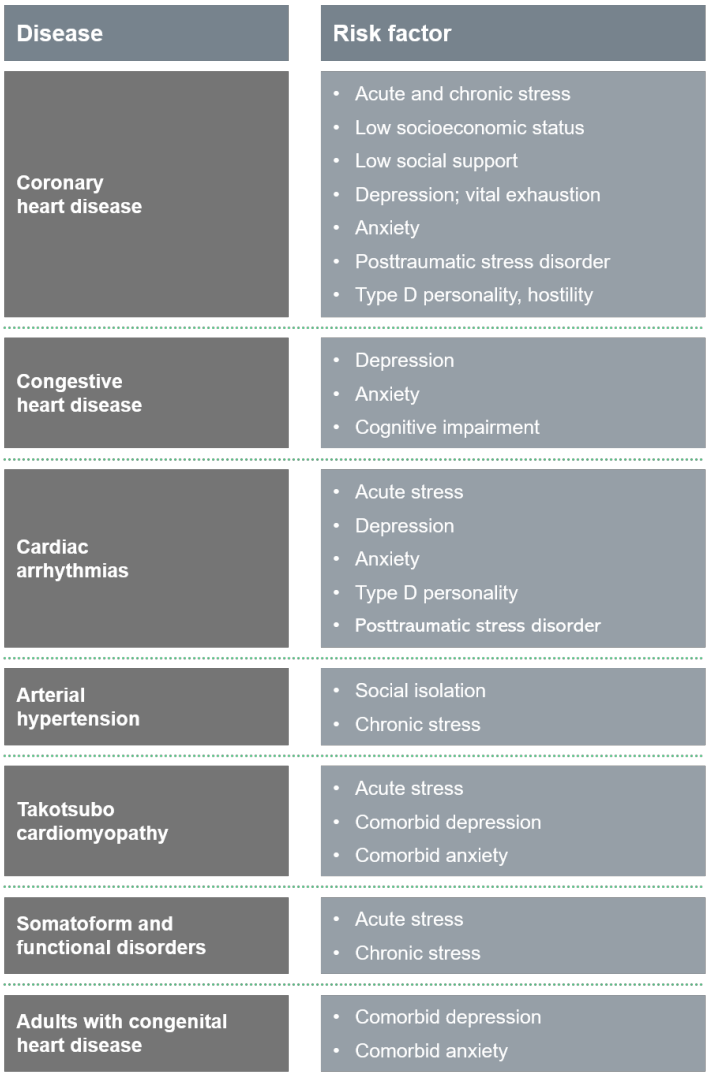

Figure 3.1: Established psychosocial risk factors in selected cardiac diseases(Albus et al., 2019)

Furthermore, several of these factors are also negatively influenced by the experience of suffering from a cardiovascular disease itself. Compared to patients with either physical or mental health problems, patients suffering from both simultaneously have dramatically reduced outcomes in all important health dimensions: they show higher mortality rates (Jünger et al., 2005; Katon et al., 2005; Lazzarino, Hamer, Stamatakis & Steptoe, 2013) as well as higher levels of symptom burden and impairment in any medical disorder index (Read, Sharpe, Modini & Dear, 2017). In addition, health care costs are significantly higher in patients with both chronic conditions and comorbid mental disorders (Lehnert, Konnopka, Riedel-Heller & König, 2011), with the higher costs largely attributable to medical, not psychosocial, care (Egede, Zheng & Simpson, 2002). The association between psychosocial factors and cardiovascular illnesses is mediated by behavioural and psycho-biological mechanisms. However, the respective factors and mechanisms are connected via complex interactions, so that the full extent of specific relationships has not yet been completely understood.

3.1.6 Medication adherence

Patients' adherence to their medication represents a crucial part of patient care and is indispensable in the pursuit of clinical goals (Lam & Fresco, 2015). In its 2003 report on medication adherence, the WHO states that '[...] increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatment' (Sabaté et al., 2003). In contrast, non-adherence leads to poor clinical outcomes, increased morbidity and mortality as well as unnecessary health care costs. Current data suggests that approximately $50\% - 60\%$ of patients are non-adherent to their prescribed medicine regimes (Svarstad, Chewning, Sleath & Claesson, 1999; McDonnell & Jacobs, 2002), especially chronic disease sufferers. Accordingly, over 30% of medicine-related hospital admissions are seen to be the result of medication non-adherence (Brown & Bussell, 2011; Johnson, Williams & Marshall, 1999). The WHO defines adherence as '[...] the extent to which the persons' behaviour (including medication-taking) corresponds with agreed recommendations from a health care provider' (Sabaté et al., 2003). This includes treatment initiation, prescribed regime implementation, and the discontinuation of the pharmacotherapy (Vrijens et al., 2012). Some studies differentiate primary or secondary adherence (Lehane & McCarthy, 2009). While primary non-adherence is understood as the frequency with which patients fail to redeem prescriptions after new medication has been prescribed, secondary non-adherence refers to patients not taking prescribed med-

ication despite having redeemed the prescription (Sackett et al., 1978; Vermeire, Hearnshaw, Van Royen & Denekens, 2001; Steiner & Earnest, 2000). Often, compliance is also used to refer to medication adherence and describes the extent to which the patients' behaviour (including medication-taking) coincides with medical or health care advice (Sabaté et al., 2003). However, it has been argued that the term may carry negative connotations as it implies passive to submissive patient behaviour. Hence, adherence will be used in this work to underline the active and feeling role patients hold in this issue. However, as Steiner and Earnest have pointed out, both terms may prove to be insufficient in describing patients' medication-taking behaviours as they may implicitly over exaggerate the physician's control over the medication process (Albus et al., 2019). According to WHO, there are multiple factors leading to poor medication adherence, normally classified into five categories: socioeconomic factors, therapy-related factors, patient-related factors, condition-related factors, and health system/health care team- (HCT-) related factors (Sabaté et al., 2003). With an understanding of whether the non-adherence is primary (initiation of pharmacotherapy) or secondary (implementation of the prescribed regime), and what factors have led to it, a proper intervention can then be tailored individually to improve the medication-taking behaviour of each patient (Lam & Fresco, 2015). Measuring adherence is, therefore, important to both researchers and clinicians. Inaccurate estimation of medication adherence can lead to several problems which are potentially costly and dangerous in both settings.

The following sections aim to provide an overview on the research base regarding selected cardiovascular diseases and specific mental health problems.

3.2 Post-traumatic stress disorder and cardiovascular disease

Criteria for the diagnosis of PTSD have evolved (North, Hong & Downs, 2018) since 1980, with changes in the definition of trauma and the addition of symptoms and symptom groups. In 2013, the American Psychiatric Association revised the PTSD diagnostic criteria in the fifth edition of its Diagnostic and Statistical Manual of Mental Disorders (Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V)) (Association, 2013). Table 3.2 summarises the current DSM-V criteria for PTSD (Association, 2013):

DSM-V criteria

Criterion A: stressor (one required)

The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, in the following way(s):

- Direct exposure
- Witnessing the trauma
- Learning that a relative or close friend was exposed to a trauma
- Indirect exposure to aversive details of the trauma, usually in the course of professional duties (e.g., first responders, medics)

Criterion B: intrusion symptoms (one required)

The traumatic event is persistently re-experienced in the following way(s):

- Unwanted upsetting memories
- Nightmares
- Flashbacks
- Emotional distress after exposure to traumatic reminders
- Physical reactivity after exposure to traumatic reminders

Criterion C: avoidance (one required)

Avoidance of trauma-related stimuli after the trauma, in the following way(s):

- Trauma-related thoughts or feelings
- Trauma-related external reminders

Criterion D: negative alterations in cognitions and mood (two required)

Negative thoughts or feelings that began or worsened after the trauma, in the following way(s):

- Inability to recall key features of the trauma
- Overly negative thoughts and assumptions about oneself or the world
- Exaggerated blame of self or others for causing the trauma

- Negative affect
- Decreased interest in activities
- Feeling isolated
- Difficulty experiencing positive affect

Criterion E: alterations in arousal and reactivity

Trauma-related arousal and reactivity that began or worsened after the trauma, in the following way(s):

- Irritability or aggression
- Risky or destructive behavior
- Hypervigilance
- Heightened startle reaction
- Difficulty concentrating
- Difficulty sleeping

Criterion F: duration (required)

- Symptoms last for more than 1 month.

Criterion G: functional significance (required)

- Symptoms create distress or functional impairment (e.g., social, occupational).

Criterion H: exclusion (required)

- Symptoms are not due to medication, substance use, or other illness.

Two specifications:

1. Dissociative Specification In addition to meeting criteria for diagnosis, an individual experiences high levels of either of the following in reaction to trauma-related stimuli:

- Depersonalisation. Experience of being an outside observer of or detached from oneself (e.g., feeling as if 'this is not happening to me' or one were in a dream).
- Derealisation. Experience of unreality, distance, or distortion (e.g., 'things are not real').

2. Delayed Specification. Full diagnostic criteria are not met until at least six months after the trauma(s), although onset of symptoms may occur immediately.

The DSM-V (Association, 2013) defines PTSD as a trauma- and stressor-related disorder precipitated by a traumatic event or life-threatening disease. PTSD is characterised by symptoms of re-experiencing aspects of the traumatic event, avoidance of places, people, and activities that are reminders of the trauma, negative cognitions and mood as well as arousal causing significant distress and functional impairment with at least one month of continuous symptoms following exposure. Post-traumatic stress symptoms experienced within the first month of the traumatic event are classified as acute stress disorder (ASD), which presents with a similar clinical picture characterised by intrusion, negative mood, dissociation, avoidance, and arousal (Association, 2013). The inclusion in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (DSM-IV; (First, 1994)) of a life-threatening disease as a potentially traumatic event that might trigger the onset of PTSD prompted a new area of research that pointed to the emergence of PTSD in the aftermath of a cardiac event.

Prevalence of post-traumatic stress disorder and cardiac mortality

The lifetime prevalence of PTSD in the U.S. is $7-8\%$ (Kessler, Berglund et al., 2005; Kessler, Sonnega, Bromet, Hughes & Nelson, 1995). Although the global prevalence of PTSD is difficult to estimate, a recent World Health Organisation study estimated a lifetime prevalence of 3% based on community samples drawn from 14 countries (largely free of conflict zones) comprising more than $20,000$ respondents (Kessler et al., 2011). Prevalence estimates are as high as 30% in populations exposed to natural and man-made disasters (Galea, Nandi & Vlahov, 2005) and combat (Weiss et al., 1992).

Our current understanding of the link between PTSD and CVD is that PTSD is likely an independent risk factor for acute cardiac events including acute coronary syndromes (i.e., myocardial infarction or unstable angina) and possibly stroke (Edmondson & von Känel, 2017; Galea et al., 2005). The association of PTSD with

CVD risk is likely carried through interacting behavioural and physiological mechanisms that relate to PTSD symptoms and, in turn, also influence CVD risk. It has also become clear that acute, potentially life-threatening CVD events can themselves cause PTSD, and that PTSD secondary to CVD events may be associated with increased risk for subsequent CVD events and mortality (Weiss et al., 1992).

Several studies have suggested the association of PTSD with incident CVD events and/or CVD death, with Hazard ratios (HRs) between 1.46 to 3.28 (Edmondson & von Känel, 2017). However, a major shortfall of these studies is that data collection was often only commenced years to decades after the original traumatic event. A recently published analysis from the Millennium Cohort Study evaluating active duty US military service members examined the effects of trauma over a shorter period. They compared self-report or medical record diagnosis of new CHD events in service members deployed on combat vs. non-combat missions, with the majority of deployments occurring shortly after the baseline study assessment (Edmondson & von Känel, 2017). Deployment was associated with a significantly increased risk of incident CHD assessed via self-report or medical record diagnoses. Furthermore, PTSD screened positive participants also showed an increased probability of self-reporting incidents but not medical record CHD diagnoses. Although there is ample evidence suggesting associations between stress, trauma, and/or PTSD and CVD risk, conclusions are limited by the shortcomings in their methodology, often only relying on self-reports or diagnostic codes from administrative databases to establish CVD events. Recently, the association of PTSD and CVD has been examined using more objective methods: in a study assessing 281 Vietnam-era veteran twin pairs, Vaccarino et al. Vaccarino (Vaccarino et al., 2013) was able to show that patients with PTSD had more than double the risk of increased incident CHD events during an average of 13 years of follow-up. Interestingly, this association proved independent of traditional CVD risk factors, such as depression and substance abuse or dependence. Moreover, the authors could show that participants with PTSD had decreased myocardial blood flow on cardiac positron emission tomography scans. Another study assessing 637 veterans without known CVD demonstrated that those with PTSD had higher levels of coronary artery calcium, a marker of atherosclerosis, on computed tomography scans (Von Känel & Orth-Gomér, 2008). It has been established that between $30\% - 70\%$ of patients with existing coronary artery disease may develop acute myocardial ischemia, measured via perfusion imaging or echocardiography, in response to psychological stressors (Bigger Jr et al., 1992).

However, with regard to life-threatening illnesses, cardiac events, and especially myocardial infarction and AMR in the wake of CTR, seem to hold unique

traumatising characteristics (Vilchinsky, Ginzburg, Fait & Foa, 2017). Features to note are the abruptness of the event, the concrete danger of death, the patients' intense sense of loss of control and experienced helplessness during the event (Kutz, Shabtai, Solomon, Neumann & David, 1994). Furthermore, Alonzo elaborates that the intrusive experience of the treatments, such as coronary surgery, angioplasty, angiography, pacemaker implantation, stress testing, and even the side effects of medications, can also be potentially traumatic events possibly resulting in the development of PTSD (Alonzo, 2000). Moreover, although cardiac disease survival rates are on the rise, it is still largely perceived as life-threatening. As a result, patients as well as their partners experience intense emotional reactions, such as fear or anxiety (of dying or recurrence), anger, sadness, and grief as well as PTSD (Fisher & Collins, 2012).

Cardiac-disease-induced post-traumatic stress disorder

Unsurprisingly, the issue of Cardiac-disease-induced post-traumatic stress disorder (CDI-PTSD) has attracted a great deal of attention, and a growing body of studies have examined its prevalence, stability, and risk factors as well as its psychological and physiological consequences (Vilchinsky et al., 2017). Over the last 20 years, evidence suggests that some cardiac patients experience Post-traumatic stress symptoms (PTSS) to the degree of warranting PTSD diagnosis (Edmondson, Kronish, Shaffer, Falzon & Burg, 2013). To date, studies researching CDI-PTSD suggest that between $12\% - 15\%$ of all patients who undergo an acute coronary event consequently develop PTSD (Vilchinsky et al., 2017; Doerfler & Paraskos, 2005; Edmondson, Richardson et al., 2012). These rates are in line with reported prevalence rates of lifetime PTSD ($8 - 1\%$, (Norris & Slone, 2007), 2014; $5 - 10\%$ (Ozer, Best, Lipsey & Weiss, 2008) as well as with PTSD rates among populations exposed to a traumatic events ($10 - 20\%$, (Norris & Slone, 2007)). Similar to PTSD of other origin, CDI-PTSD has been associated with high levels of negative outcomes among patients (Spindler & Pedersen, 2005). About half of the studies (Vilchinsky et al., 2017) reviewed were conducted on patients following an myocardial infarction, whereas the minority of studies focused on patients who had experienced cardiac arrest or had undergone specific medical procedures (e.g., cardiac surgery, heart transplantation). Comparing the rates of CDI-PTSD across illnesses, diagnoses and procedures revealed that cardiac arrest yielded the highest CDI-PTSD prevalence, followed by the other cardiac-disease-related diagnoses and invasive procedures, among which the prevalence of CDI-PTSD was similar. Given the fact that individuals who have undergone a cardiac arrest have, in a way, experienced death, this finding is not surprising. Yet we should view this prevalence hierarchy with

caution since very few studies have focused specifically on cardiac arrest patients (Vilchinsky et al., 2017). Overall, findings show that rates of CDI-PTSD are relatively stable over time, though a trend toward recovery exists. A small group of cardiac patients exhibited chronic CDI-PTSD; and not enough data has been accumulated regarding delayed PTSD – the development of CDI-PTSD symptoms after an initial period in which patients were asymptomatic, or at least without a clinical-level CDI-PTSD (Hari et al., 2010). Similar trends of fluctuations in PTSD over time have been observed in survivors of other types of trauma such as accidents (Carty, O'donnell & Creamer, 2006) and war (Andersen, Karstoft, Bertelsen & Madsen, 2014).

3.2.1 Prevalence

The current section focuses on the studies conducted on ACS patients (mostly myocardial infarction); therefore, the terms 'MI', 'CDI (cardiac-disease-induced)', and 'ACS' will be used interchangeably. CDI-PTSD in this population was assessed at various time points along the course of the illness, from hospitalisation (e.g.(Castilla & Vázquez, 2011) to as many as 30 years later (e.g.(Chung, Dennis, Berger, Jones & Rudd, 2011). Very few studies have focused on the manifestation of CDI-PTSD symptoms during hospitalisation or within the first two weeks of the myocardial infarction (defined as acute stress disorder, or ASD). These studies presented a large variability in the prevalence of MI-induced ASD, ranging from $0\% - 26\%$ (e.g.(Castilla & Vázquez, 2011; Gao, Zhao, Li & Cao, 2015; Ginzburg et al., 2003; Meister et al., 2016; Oflaz et al., 2014; Sheldrick, Tarrier, Berry & Kincey, 2006). An examination of these studies revealed that the prevalence of ASD was a function of the measurement used. When ASD was diagnosed by clinical interview (Roberge, Dupuis & Marchand, 2008; van Driel & den Velde, 1995), ASD rates were lower than those emerging from studies which used self-report questionnaires (e.g. (Gao et al., 2015; Ginzburg et al., 2003; Neumann, 1991)). The same pattern was observed in studies that examined CDI-PTSD rates one month after the myocardial infarction (e.g. (Roberge et al., 2008; Rocha et al., 2008; Edmondson et al., 2011; Pedersen, Middel & Larsen, 2002; Sumner et al., 2015). Finally, studies in which both interviews and self-report questionnaires were applied showed that data collected by self-report yielded higher rates of CDI-PTSD than did data collected via interview (Guler et al., 2009; Rocha et al., 2008; Wiedemar et al., 2008). Reported rates of PTSD within three to 18 months after the myocardial infarction ranged from $3\% - 21\%$ (e.g.(Castilla & Vázquez, 2011)). These variations in the reported rates may be attributed to a) the difference in sample sizes which in some studies was 50

and lower (e.g.(Bennett & Brooke, 1999; Castilla & Vázquez, 2011; Doerfler, Pbert & DeCosimo, 1994; Girard et al., 2007)) and/or b) changes in the defining criteria for PTSD (e.g., a change in cutoff scores: see, for example, (Shemesh et al., 2001, 2004). Only a few studies have assessed CDI-PTSD for a period that was longer than 18 months. For example, Van Driel and Den Velde (1995) interviewed 18 myocardial infarction patients two years post-MI using the structured clinical interview for the diagnosis of PTSD (SCID-R-PTSD), and none of the participants was diagnosed as having PTSD (Vilchinsky et al., 2017). Wikman, Bhattacharyya, Perkins-Poraz, and Steptoe (2008), who evaluated 179 myocardial infarction patients three years post-MI using self-report questionnaires(Wikman, Bhattacharyya, Perkins-Porras & Steptoe, 2008), classified 13% as havingPTSD. The same rate (13.3%), on the basis of a self-report questionnaire (PTSD Inventory; (Solomon et al., 1993), was reported by Ginzburg and Ein-Dor (Ginzburg & Ein-Dor, 2011) in a sample of myocardial infarction patients eight years post-MI. In order to pinpoint the differences in CDI-PTSD prevalence according to the instrument used, Einsle, Kraft, and Kollner (Einsle, Kraft & Köllner, 2012) focused specifically on comparing different diagnostic tools for PTSD among CAD, heart transplantation and cardiac arrhythmia patients, but again found limited agreement between self-report measures (e.g., Impact of Events Scale-IES-R; (Horowitz, Wilner & Alvarez, 1979); The Post-Traumatic Stress Syndrome 10-Questions Inventory-PTSS-10; (Stoll et al., 2000)) and the SCID (Structured Clinical Interview for DSM-IV-TR; (First, Spitzer, Gibbon, Williams & others, 2002)APA, 2002). As in the aforementioned studies, the prevalence of CDI-PTSD ranged from $15\% - 48\%$ when the PTSS-10 was applied, from $5\% - 12\%$ when the IES-R was applied, and only from $1.7\% - 9.8\%$ when the SCID was used. The vast variance in interval times $-$ between index event and follow-up $-$ should be taken into consideration, however, as they differed greatly among each of the diagnostic groups (ranging from two months to seven years). In a recent review paper, Edmondson, Richardson, et al. (Edmondson, Shaffer, Denton, Shimbo & Clemow, 2012) and Edmondson, Shaffer, et al. (Edmondson, Richardson et al., 2012) suggested an aggregated prevalence estimate of 12% (95% CI, $9\% - 16\%$) for clinically significant symptoms of ACS-induced PTSD. Overall, the prevalence estimate was 16% when self-report instruments were used, while the clinical diagnostic interview yielded a prevalence estimate of 4%.

3.2.2 Risk factors for Cardiac-disease-induced post-traumatic stress disorder

In some studies, a younger age (i.e., early illness onset) was shown to be a risk factor for PTSD (e.g., (Bennett & Brooke, 1999; Dinenberg, McCaslin, Bates & Cohen, 2014)). Other studies, however, did not find any age effect (e.g. (Roberge et al., 2008)), or showed an opposite effect (Gao et al., 2015). This inconsistency in findings was also detected with regard to gender. Some studies found that female myocardial infarction patients were more prone to develop PTSD than male myocardial infarction patients (Hari et al., 2010; Brancu et al., 2016). Other studies did not find any gender differences (e.g. (Marke & Bennett, 2013; Wikman et al., 2012)), or found that male patients were at higher risk for PTSD than female patients (Gao et al., 2015). Ethnicity was also shown to be a risk factor in some studies (e.g. (Kutz et al., 1994), (Wikman et al., 2008)), but not in others (e.g. (Ayers, Copland & Dunmore, 2009; Wikman, Molloy, Randall & Steptoe, 2011)). Finally, all but one study (Wikman et al., 2008) found no effect for socio-economic status (SES) (e.g. (Ginzburg et al., 2003; Kutz et al., 1994; Whitehead, Perkins-Porras, Strike & Steptoe, 2006; Wikman et al., 2011, 2012)). Other demographic variables including marital status, cohabitation, number of children, income, education, employment, and religion were found to be unrelated to CDI-PTSD (e.g. (Ayers et al., 2009; Dinenberg et al., 2014; Edmondson et al., 2011; Ginzburg et al., 2003; Kutz et al., 1994; Roberge et al., 2008)). Thus, no demographic variable was consistently found to be a reliable risk factor for CDI-PTSD(Vilchinsky et al., 2017). In other areas of post-trauma, however, the following variables were found to be reliable risk factors for PTSD: female gender, younger age, racial/ethnic minority status, and lower intelligence (e.g. (Brewin, Andrews & Valentine, 2000)). This discrepancy may be attributed to some of the specific characteristics of cardiac disease (i.e., a higher prevalence of male patients than female patients, who have their first cardiac episode at a younger age than women do (Bjarnason-Wehrens, Grande, Loewel, Völler & Mittag, 2007)). The most consistent risk factor found for CDI-PTSD − as has also been found for PTSD resulting from other ('traditional') events ((King et al., 2012)) − was psychological functioning, whether it was conceptualised as premorbid distress, distress during the event, or premorbid personality difficulties. Focusing on medical- and illness-related putative risk factors, it was the perceived severity rather than the objective severity which was associated with the development of CDI-PTSD. This finding corresponds with numerous findings in the health psychology field attesting to the more important role played by perceived illness severity than by objective illness severity in terms of determining both patient dis-

tress and adherence ((DiMatteo, Haskard & Williams, 2007; Grigioni et al., 2003; Naidoo & Wills, 2000)). CDI-PTSD was found to be associated with a wide range of negative physical and emotional consequences, from overall psychopathology to mortality. Since most studies reviewed were either cross-sectional or retrospective, however, it was often difficult to differentiate the consequences of CDI-PTSD from its risk factors. Yet the findings regarding elevated levels of mortality and cardiac events associated with CDI-PTSD are worthy of continued study, considering the world-wide prevalence of cardiac disease.

3.2.3 Physiological factors

Additional biological mechanisms may be responsible, including increased activity in the hypothalamic pituitary adrenal axis, autonomic nervous system reactivity, inflammation, oxidative stress, and endothelial dysfunction. There is strong evidence that these changes occur in response to chronic, daily stressors as well as traumatic events and PTSD, but it remains to be seen whether they are responsible for the associations of stress/trauma and CVD (Gill, Saligan, Woods & Page, 2009).

3.2.4 Treatment

Though more psychologically oriented CVD prevention trials have first and foremost focused on reducing depressive symptoms, some evidence for the protective effects of stress reduction on CVD risk is available. Previous small trials found that a variety of psychosocial interventions reduced the risk of recurrent CVD events when added to traditional cardiovascular rehabilitation programs (Linden, Stossel & Maurice, 1996). More recent large trials with carefully selected control groups have provided further support. Gulliksson et al. (Gulliksson et al., 2011) randomised 362 men and women with a CHD event in the last year to standard care that included control of traditional cardiovascular risk factors or to standard care plus a 20-session cognitive behavioural therapy intervention focused on stress management. Over a mean follow-up period of 7.8 years, the stress management group had significantly fewer recurrent CVD events (HR : 0.59, 95% CI : 0.42-0.83) and myocardial infarctions (HR : 0.55, 95% CI : 0.36-0.85). Another recent trial comparing transcendental meditation to health education in 201 black men and women with CHD found the meditation group had a significant reduction in a combined endpoint of all-cause mortality, myocardial infarction, or stroke over a mean of 5.4 years (HR : 0.52, 95% CI : $0.29 - 0.92$) (Schneider et al., 2012). Additional studies are needed to examine the effects of stress reduction for primary prevention of CVD as well as to explore treatments in patients with PTSD. How-

ever, these prior studies suggest that psychological stress is a reasonable target for CVD prevention.

However, while traumatic conditions within the spectrum of acute coronary syndrome and potentially traumatic cardiological treatment procedures (e.g., defibrillator implantation) have been at the centre of research efforts, the relationship of PTSD and CTR has not received any attention so far.

3.3 Depression and cardiovascular disease

Depression and anxiety are the most frequent disorders accompanying somatic diseases. Depressive disorders are predominantly characterised by persistent depressive mood combined with loss of interest, pleasure, and energy . With a lifetime prevalence of up to 24% for major depressive episodes ((Ferrari et al., 2013; Kessler, Chiu, Demler & Walters, 2005)), depressive disorders represent one of the most frequent types of psychiatric disorders. More common in females, depressive disorders are associated with a significant impairment of quality of life ((Saarni et al., 2007)) and high psychological strain, including suicidal ideation and behaviour ((Hardy, 2009; Scott et al., 2007).

3.3.1 Prevalence of depression and cardiac mortality

Major depression is a highly prevalent condition, affecting approximately 10% of the population (Kessler, Chiu et al., 2005). It is also a growing global problem (Whiteford et al., 2013), and has been consistently associated with increased risk of CHD (Carney & Freedland, 2017). It is therefore not surprising that depression is highly comorbid with CHD: Major depression is two to three times more common among patients with CHD than in the general population. The prevalence of depression is $15 - 30\%$ in patients with CHD (Lichtman et al., 2014), and is approximately twice as high in women than men, especially affecting young women in the aftermath of acute myocardial infarction (Vaccarino & Bremner, 2017).

3.3.2 Risk factors

Depression as a risk factor for CHD has been characterised from mild depressive symptoms to a clinical diagnosis of major depression. As defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), clinical depression, or major depression, is characterised by depressed mood or anhedonia (loss of interest or pleasure) for at least 2 weeks accompanied by significant

functional impairment and additional somatic or cognitive symptoms (Association, 2013). Most epidemiological studies of depression and incidence of CHD have used depressive symptom scales, and have frequently demonstrated a dose−response pattern, with higher levels of depressive symptoms being associated with higher risk (Carney & Freedland, 2017).

The exact mechanisms linking depression to increased CHD risk are complex and multi-factorial, and still incompletely understood (Carney & Freedland, 2017). Although adverse lifestyle behaviours and traditional CHD risk factors, such as smoking and sedentary lifestyle, largely contribute to the risk, they do not explain it entirely. In CHD patients, depression is also associated with severity of functional impairment, lower adherence to therapy and lower participation in cardiac rehabilitation. Whether and to what extent these factors explain the relationship between depression and CHD deserves future study. The present paper summarises key aspects in our current knowledge, linking depression and CHD within the intersecting fields of neuroscience, cardiovascular physiology, and behavioural medicine. It is our objective of bringing attention to this area and stimulating interdisciplinary research, clinical awareness, and improved care (Vaccarino et al., 2019).

3.3.3 Depression and coronary heart disease

As stated above, many studies have shown a relationship between major depression, or depressive symptoms, and CHD (Carney & Freedland, 2017; Meijer et al., 2011; Gan et al., 2014). This literature has been summarised by a number of meta-analyses (Meijer et al., 2011; Gan et al., 2014; Nicholson, Kuper & Hemingway, 2006), all providing evidence for an association between clinical depression (or depressive symptoms) and CHD. This link is seen in individuals initially free of CHD and in a variety of CHD patient populations, including patients with ACS, heart failure, stable CHD, and post-coronary bypass surgery. However, individual studies have produced heterogeneous risk estimates and have varied in their ability to adjust for other factors such as smoking, physical inactivity, other risk factors, and severity of CHD (Vaccarino et al., 2019). Indeed, depression is associated with several CHD risk factors and health behaviours as described above. In statistical models that adjust for these risk factors, depression usually remains an independent risk factor for CHD, suggesting a biological relationship between these two disease states that remains in part unexplained by an increase in traditional risk factors or lifestyle behaviours. In one of the relatively recent meta-analyses, which included 30 prospective cohort studies of individuals initially free of CHD, depres-

sion was associated with a 30% increased risk of future coronary events (Gan et al., 2014). The association remained significant in the group of studies that adjusted for socio-demographic factors and lifestyle behaviours (Meijer et al., 2011). In community samples and in general practice clinics, the rate of depression is about, $10 - \%11$ but it goes up to about $15 - 30\%$ in patients with CHD (Cassano & Fava, 2002; Ziegelstein, 2001). Studies have also suggested that specific subtypes of depression may be more strongly associated with CHD risk than others. For instance, patients with a new onset of depression after ACS, with treatment-resistant depression, or with somatic depressive symptoms as opposed to cognitive symptoms, are all at increased risk of developing adverse CHD outcomes. However, there is no clear consensus on whether these different phenotypes carry variations in risk (Freedland & Carney, 2013).

Gender differences

Among women, depression is approximately twice as prevalent as in men and has shown some of the most robust associations with CHD (Vaccarino, 2015). Depression in women is also on average more severe than in men and has an earlier age of onset. Women with CHD similarly have twice the rates of depression as men with CHD (Mallik et al., 2006; Vaccarino et al., 2014; Smolderen et al., 2015). The condition is especially common in young women who have survived a myocardial infarction (Mallik et al., 2006; Vaccarino et al., 2014, 2018) about half of women younger than 60 years with a previous myocardial infarction have a history of major depression (Vaccarino et al., 2014; Smolderen et al., 2015; Vaccarino et al., 2018). Of note, young women are more likely to die of myocardial infarction than men (Cenko et al., 2018). Depression is linked to early life adversities and psychological trauma, which tend to be more common in girls than boys and may result in chronic dysregulation of neurohormonal stress systems. This may begin at an early age, setting the stage for an increase in cardiovascular risk in women many years before CHD becomes manifest (Vaccarino & Bremner, 2017).

Among women, depression increases their risk for CHD between 30% and twofold depending on depression measures and CHD endpoints (Wassertheil-Smoller et al., 2004; Whang et al., 2009). Two follow-up studies of young community samples (< 40 years old) found that the impact of depression on CHD risk was higher among women than men (A. J. Shah, Veledar, Hong, Bremner & Vaccarino, 2011; Wyman, Crum & Celentano, 2012). In the Third National Health and Nutrition Examination Survey (NHANES III), a history of major depression or suicide attempt was associated with almost 15-fold increased risk of ischaemic heart disease among women, and 3.5 in men (A. J. Shah et al., 2011). In the prospective Com-

munity Mental Health Epidemiology Study of Washington County, mean (MD), women younger than 40 years with depression had a six-fold increased risk of CHD compared with women of the same age without depression, while depression was not associated with CHD in men or older individuals (Wyman et al., 2012). Even among patients referred for coronary angiography, depression is more predictive of adverse cardiovascular outcomes in young women than in other groups (A. J. Shah et al., 2014). After an acute myocardial infarction, however, depression seems to affect prognosis to a similar extent in women and men (Parashar et al., 2009). Overall, the evidence suggests that depression is more closely associated with CHD for women than for men, with the strongest effects for younger women.

Depression as a prognostic factor in acute coronary syndromes

Despite some heterogeneity of findings, the bulk of the evidence supports the notion that depression after ACS is a risk factor for all-cause and cardiac mortality, as well as for composite outcomes including mortality or non-fatal cardiac events (Lichtman et al., 2014). Among patients hospitalised for ACS, the increased risk occurs regardless of whether depression pre-dated the ACS event or developed subsequently (Lichtman et al., 2014; Parashar et al., 2006; LEUNG et al., 2012). However, some evidence suggests that depressive episodes that develop soon after an ACS may carry a higher risk than episodes that begin before the event (Spijkerman et al., 2005; Carney et al., 2009; Peter de Jonge, van den Brink, Spijkerman & Ormel, 2006). Depression is also a major determinant of unplanned hospitalisations within 30 days after a hospital discharge for myocardial infarction (Hess et al., 2016).

Some studies have found that the somatic symptoms of depression may carry a higher risk than cognitive symptoms (Martens, Hoen, Mittelhaeuser, de Jonge & Denollet, 2010; Smolderen et al., 2009; de Jonge et al., 2006). Depressive episodes that do not respond to standard treatments have also been identified as high-risk subtypes (Carney & Freedland, 2009). However, evidence suggests that recognition and treatment of depression improves prognosis. In a previous study, patients with depression that was recognised or treated during an myocardial infarction hospitalisation or at discharge had similar 1-year mortality than those without depression, while a higher mortality was confined to patients with untreated depression (Smolderen et al., 2017). These data are important since depression in ACS patients is frequently under-recognised and untreated (Smolderen et al., 2009; Huffman et al., 2006; Cepoiu et al., 2008).

Patients with comorbid depression and CHD have lower adherence to treatments and lifestyle changes; for example, they are significantly less likely to adhere to medication regimens (Gehi, Haas, Pipkin & Whooley, 2005; Benner et al., 2002)

to follow lifestyle recommendations (e.g. smoking cessation, exercise), and practice self-management (e.g. weight monitoring in heart failure) (Rumsfeld & Ho, 2005). They are also less likely to participate in cardiac rehabilitation programmes and more likely to drop out of these programmes (Gehi et al., 2005; Swardfager et al., 2011; Blumenthal, Williams, Wallace, Williams Jr & Needles, 1982). Improvement in depression is associated with better self-reported adherence to medications and secondary prevention lifestyle (Hare, Toukhsati, Johansson & Jaarsma, 2014; Bauer et al., 2012).

During the first year post-MI, the presence of depression is associated with about 40% higher health-care costs, including outpatient care and hospital re-admissions (Frasure-Smith et al., 2000). In addition, the presence of major depression in the past 12 months can affect societal costs indirectly through work absence (Stein, Cox, Afifi, Belik & Sareen, 2006). For all the above reasons, major depression has been proposed as a risk factor for adverse medical outcomes in patients with ACS (Lichtman et al., 2014). The application of collaborative care interventions for depression in CHD populations has emerged as a promising health-care model to reduce the societal impact of this common comorbidity (Katon et al., 2010; P. J. Tully & Baumeister, 2014).

3.3.4 Physiological factors

The well-documented association between depression and CHD has prompted a search for underlying mechanisms. One possibility is that changes in neurobiology in depressed patients alter cardiovascular function and structure (Burg & Soufer, 2014; Soufer Robert, 2004; Vaccarino & Bremner, 2013). Additionally, because of the known link between stressful exposures and depression, (Kendler, Thornton & Gardner, 2000) dysregulation of stress-response pathways may contribute to CHD in vulnerable individuals. Thus, neuro-biological mechanisms associated with stress and depression may be relevant for CHD risk. These mechanisms include changes in sympathetic nervous system and neurohormonal function as well as alterations in central brain function (Veith et al., 1994; Carney et al., 1999).

3.3.5 Behavioural factors

Although positive behaviour changes for primary and secondary prevention of CHD are recommended (Piepoli et al., 2016), a sizeable proportion of patients do not make any changes (McBride et al., 2008). One factor that may shape individuals' responses to a health behaviour change is their emotional state, such as the presence of depression. Prior studies have extensively documented the associ-

ation of depression with adverse health behaviours, including smoking (Mykletun, Overland, Aarø, Liabø & Stewart, 2008), excessive drinking, (Levola, Holopainen & Aalto, 2011) physical inactivity, and overeating (Ferrer-Garcia et al., 2017; Bruch, 1964; van Strien, Peter Herman & Verheijden, 2012). For example, depression is associated with an increased risk of becoming a smoker, with an increased rate of daily smoking, and with a lower probability of quitting smoking (Breslau, Peterson, Schultz, Chilcoat & Andreski, 1998; Fergusson, Goodwin & Horwood, 2003; Anda et al., 1990; Hall, Muñoz, Reus & Sees, 1993). Depression is also associated with overweight and obesity, and with approximately 40% higher risk of developing Type 2 diabetes (Petri et al., 2017; Mason & Lewis, 2014; Lee et al., 2017; Pine, Goldstein, Wolk, Weissman & others, 2001; Goodman & Whitaker, 2002; Kawakami, Takatsuka, Shimizu & Ishibashi, 1999; Golden et al., 2004; Arroyo et al., 2004). Some of these associations appear bidirectional (Pan et al., 2010, 2012). Obesity and other cardiometabolic risk factors have been linked to increased oxidative stress, inflammation, and microvascular dysfunction (Badimon et al., 2017; Sorop et al., 2017; Ngo et al., 2014), which lend further support for a central role of inflammation and microvascular disease as possible links between cardiometabolic disturbances, depression and CHD (Vaccarino et al., 2009, 2008; Capuron et al., 2008; Agtmaal, Houben, Pouwer, Stehouwer & Schram, 2017).

3.3.6 Treatment of depression in patients with cardiovascular disease

There are several treatments options for the CHD patient with depression, from medications to various forms of psychotherapy, to exercise and stress management approaches. Although treatment of depression has not been shown to improve cardiovascular outcomes in CHD patients, depression should still be addressed if severe enough, in order to promote patient wellness and Quality of life (QoL). Tricyclics should be avoided in this patient population.

3.3.7 Psychotherapeutic treatment

A number of interventions can be useful for CHD patients with depression. Psychotherapy helps people with depression understand the behaviours, emotions, and ideas that contribute to depression, regain a sense of control and pleasure in life, and learn to apply coping skills (Hirschfeld, 2012). Psychodynamic therapy is based on the assumption that a person is depressed because of unresolved, generally unconscious conflicts, often stemming from childhood. Interpersonal

therapy focuses on patients' behaviour and interactions with family and friends. The primary goal of this therapy is to improve communication skills and increase self-esteem during a short period of time. Cognitive Behavioural Therapy (CBT) involves examining thought patterns that can be negative and self-defeating, and going over the basis of such thoughts and how they contribute to negative emotions. Other therapies useful for depression include stress management and stress reduction techniques, such as deep breathing, progressive muscle relaxation, yoga, meditation, and mindfulness-based stress reduction. These interventions can be provided in group format or individually by trained personnel. Psychotherapy has been shown to be equally effective for depression as medications, and some people, especially with early life stress issues, may not respond to medication without psychotherapy.

The Enhanced Recovery in Coronary Heart Disease Patients (ENRICHD) trial could not demonstrate a benefit for CBT, with medication intervention for severe depression, for the improvement of cardiac outcomes in depressed or socially isolated patients with CHD (Berkman et al., 2003). The effects of the intervention on depression, however, were modest, and patients who responded to treatment did have a better outcome than those who did not respond (Freedland & Carney, 2013). Unanswered questions, therefore, remain on whether treatment of depression may improve CHD outcomes.

3.3.8 Pharmacological treatment

Antidepressant medications are a useful tool for the treatment of depression in patients with CHD, especially those with moderate-to-severe depression (Davis, Hamner & Bremner, 2016; Fournier et al., 2010). Antidepressants act on the serotonin, dopamine, and norepinephrine systems and other neurotransmitter circuits in the brain.

However, while depressive conditions and CHD have been at the centre of many important research efforts, the relationship of depressive disorders and CTR has not received any attention so far.

3.4 Anxiety disorders and cardiovascular disease

Anxiety is characterised by transient fear, uncertainty, and apprehension about the future (Cervellin et al., 2016). Individuals vary on the frequency and intensity with which they experience anxiety (Barlow, 2004). When an individual experiences anxiety frequently, at high intensities, and/or in inappropriate situations,

they may then be diagnosed with an anxiety disorder, including generalised anxiety disorder, panic disorder, phobias, and others(Barlow, 2004). Resulting avoidance behaviour and social withdrawal are very resistant to spontaneous recovery without specialised treatment (Celano, Daunis, Lokko, Campbell & Huffman, 2016; Nikendei, Kindermann, Junne & Greinacher, 2019). Of note, DSM-V, reclassified PTSD as a 'trauma and stressor-related disorder' rather than an anxiety disorder. In the United States, the lifetime prevalence of any anxiety disorder is greater than 25% (Kessler, Berglund et al., 2005).

Generalised Anxiety Disorder

General anxiety disorder is highly prevalent in patients with cardiac disease (Celano et al., 2016). A recent meta-analysis found an 11% point prevalence and 26% lifetime prevalence of General anxiety disorder in CAD patients (P. J. Tully & Cosh, 2013). A similar meta-analysis in HF patients found General anxiety disorder prevalence to be 14% (Easton, Coventry, Lovell, Carter & Deaton, 2016). These rates are significantly higher than the $3-7\%$ lifetime prevalence of General anxiety disorder in the general US population (Hoge, Ivkovic & Fricchione, 2012; Kessler, Chiu et al., 2005).

GAD is independently associated with poor outcomes in patients with established cardiac disease, especially CAD. Though one study found that General anxiety disorder was protective in the post-ACS period (Parker, Hyett, Hadzi-Pavlovic, Brotchie & Walsh, 2011), most studies suggest that General anxiety disorder is associated with poor cardiac health in all stages of CAD (Frasure-Smith & Lespérance, 2008; Roest, Zuidersma & de Jonge, 2012; P. J. Tully, Winefield et al., 2015). Following myocardial infarction, General anxiety disorder has been linked to a nearly twofold increased risk of mortality over the subsequent 10 years (Roest et al., 2012), and in patients with stable CAD, General anxiety disorder is associated with a twofold increased risk of major adverse cardiac events over the next 2 years (Frasure-Smith & Lespérance, 2008). In a prospective study of 158 patients undergoing CABG surgery, General anxiety disorder was associated with incident major adverse cardiac events over the subsequent 5 years (P. J. Tully, Winefield et al., 2015). The associations between General anxiety disorder and outcomes in HF have not yet been studied (Bankier, Barajas, Martinez-Rumayor & Januzzi, 2008).

Panic Disorder

panic Disorder (PD) also is common in patients with heart diseases. Among patients with CAD, studies have varied results for prevalence: one review provides

PD prevalence estimates of $10-50\%$ (Fleet, Lavoie & Beitman, 2000), another analysis and a recent cross-sectional study estimate PD prevalence of $5-8\%$ in patients with established CAD (Todaro, Shen, Raffa, Tilkemeier & Niaura, 2007). These latter studies are likely closer to the true estimate, as a study of post-ACS patients found PD to be significantly less prevalent than General anxiety disorder or depression (Celano, Suarez, Mastromauro, Januzzi & Huffman, 2013).

While less common than General anxiety disorder, PD significantly increases the risk of the development and progression of cardiac disease. In a cohort study of nearly $80,000$ individuals without pre-established CAD (and half with PD), PD was associated with a nearly twofold increased risk of incident CAD (Gomez-Caminero, Blumentals, Russo, Brown & Castilla-Puentes, 2005). In another cohort study of $57,615$ patients with PD and nearly $350,000$ age- and sex-matched controls, patients with PD had a significantly higher risk of the development of CAD, but a lower risk of CAD-related mortality (Walters, Rait, Petersen, Williams & Nazareth, 2008). Finally, a systematic review and meta-regression analysis of over 1 million patients found that PD was significantly associated with incident CAD, major adverse cardiac events, and myocardial infarction (P. Tully et al., 2015).

3.4.1 Prevalence of anxiety disorders and cardiac mortality

Relative to psychological stress and trauma (Richardson et al., 2012) and depression, (Nicholson et al., 2006) less is known about the association of anxiety and anxiety disorders with cardiovascular risk. In a 2010 meta-analysis of 20 studies ($N = 249,846$) assessing the association of anxiety (i.e., anxiety, panic, phobia, post-traumatic stress, and worry) with incident CHD, Roest et al. (Roest, Martens, de Jonge & Denollet, 2010) found that initially healthy individuals with high anxiety were at increased risk for incident CHD ($HR: \ 1.26; \ 95\% \ CI: \ 1.15-1.38; \ P < 0.0001$) and cardiac death ($HR: 1.48; \ 95\% \ CI: \ 1.14-1.92; \ P = 0.003$), independent of demographic variables, biological risk factors, and health behaviours. Although studies of post-traumatic stress were included, no significant differences in effect size estimates were found by anxiety type, suggesting that PTSD did not account for the significant meta-analytic estimate. However, the meta-analytic estimate for the association of anxiety with CHD was not adjusted for depression, which is highly comorbid with anxiety. More recently, 2 large prospective national registry studies have reported on the association of anxiety with incident CHD. In a study of (Crum-Cianflone et al., 2014), 321 men who were assessed for anxiety prior to military service, any anxiety disorder diagnosis was strongly associated with incident CHD and acute myocardial infarction over 37 years of follow-

up (*multivariate adjusted HR* : 2.17 (95% *CI* : $1.28 - 3.67$) *and* 2.51 (95% *CI* : $1.38 - 4.55$), respectively) (Janszky, Ahnve, Lundberg & Hemmingsson, 2010). Another prospective cohort study of (Berkman et al., 2003), 895 Finnish men and women reported a significant association of anxiety with elevated risk of incident CHD over 7 years of follow-up(Nabi et al., 2010). However, after adjustment for confounders and concurrent depression, the only remaining signal of an association of anxiety with fatal and nonfatal CHD was in women, with *HR* : 1.24; 95% *CI* : $0.91 - 1.70$ per unit increase in anxiety symptoms. Further, the anxiety scale assessed somatic symptoms such as palpitation without exercise, irregular heartbeat, chest pain upon anger or emotion, sweating without exercise, and flushing which may themselves be symptoms of cardiovascular abnormalities that predisposed patients to cardiovascular events rather than due to anxiety, alone(Cohen, Edmondson & Kronish, 2015). The association of anxiety with adverse outcome in patients with existing CHD is similarly mixed. For example, in some studies generalised anxiety disorder is associated with increased risk for recurrent events and mortality ($HRs = 1.7 - 1.9$) (Martens, de Jonge et al., 2010; Roest et al., 2012), but others have found no association, (Versteeg et al., 2013) or even a protective effect for this anxiety disorder (Parker et al., 2011).

3.4.2 Behavioural factors

Although the true association between anxiety/anxiety disorders and CVD is unclear, a number of pathways by which anxiety may influence CVD onset or progression have been proposed. For example, anxiety is associated with poorer health behaviours, such as cigarette smoking, excess alcohol consumption, lower physical activity (Strine, Chapman, Kobau & Balluz, 2005), and poor diet (Antonogeorgos et al., 2012), which increase the risk of CVD. Interestingly, anxiety has not been clearly associated with medication non-adherence (DiMatteo, Lepper & Croghan, 2000).

3.4.3 Treatment of anxiety disorders in patients with cardiovascular disease

Anxiety disorders are common, and should be treated with pharmacotherapy and cognitive behavioural therapy, based on the substantial quality of life burden they represent. Although anxiety disorders may contribute to cardiovascular risk, and may set the stage for emotionally triggered acute events in particular, currently no study has demonstrated whether treating anxiety disorders offsets cardiovascu-

lar risk. Thus, based on current evidence, clinicians should focus on assessing and treating anxiety disorders in cardiovascular patients as an approach to improving the quality of life of their patients (Celano et al., 2016).

3.4.4 Risk factors

Health behaviours may explain part of the link between anxiety disorders and cardiac health. Adherence to a number of healthy behaviours, such as maintaining a healthy diet, healthy level of physical activity, and medication adherence, is clearly linked to improved outcomes in patients with cardiac disease (Duncan & Pozehl, 2003; Kronish & Ye, 2013; McDermott, Schmitt & Wallner, 1997). Further, for patients with stable HF or following myocardial infarction, attendance at cardiac rehabilitation programs is an important step to improving health-related-quality of life (HRQoL) and reducing the risk of future hospitalisation (Anderson & Taylor, 2014). In contrast, unhealthy behaviour can lead to the development or worsening of risk factors including diabetes, hypertension, elevated cholesterol, obesity, and smoking, all which increase mortality in patients with cardiac disease (Stamler et al., 1993).

Though the evidence is mixed, individuals who experience anxiety appear less likely to engage in health behaviours. Anxious individuals tend to have an increased dietary cholesterol intake and total energy intake, a sedentary lifestyle, and decreased physical activity (Bonnet et al., 2005). This is consistent with the finding that patients with PD and General anxiety disorder have increased odds of dyslipidemia, obesity, diabetes, and substance use (Kinley et al., 2015; Simon et al., 2006). Patients with PTSD have poor diet quality (with most energy obtained from fatty acids), decreased physical activity, increased obesity, and increased rates of smoking (Gavrieli, Farr, Davis, Crowell & Mantzoros, 2015). Among cardiac patients, anxiety is associated with a lower likelihood of adhering to a number of risk-reducing recommendations after myocardial infarction, including smoking cessation, social support utilisation, and stress reduction (Kuhl, Fauerbach, Bush & Ziegelstein, 2009). Patients with anxiety disorders also are less likely to both attend and complete cardiac rehabilitation programs (Zolnierek & DiMatteo, 2009; Lane, Carroll, Ring, Beevers & Lip, 2001). These behavioural factors in patients with anxiety disorders could increase the likelihood of cardiovascular morbidity and mortality.

3.4.5 Diagnosis and treatment of anxiety disorders in patients with cardiovascular disease

Diagnosing anxiety disorders in patients with cardiovascular disease is difficult given the substantial overlap between the symptoms of anxiety disorders and those of cardiovascular disease. Many symptoms of General anxiety disorder, such as restlessness, fatigue, poor concentration, and sleep disturbance, are very common in patients with cardiac disease, especially HF. Similarly, nearly all the symptoms of a panic attack (e.g., palpitations, diaphoresis, dyspnea, nausea, chest pain) could potentially be experienced in the setting of an arrhythmia, ACS, or paroxysmal nocturnal dyspnea. If one relies too heavily on these overlapping symptoms, there is a significant risk of attributing cardiac symptoms to anxiety (Celano et al., 2016).

Psychotherapy

Psychotherapy, especially CBT, is a reasonable alternative to pharmacotherapy in cardiac patients and in some cases may be preferable to pharmacologic treatment. In contrast to antidepressant and anxiolytic medications, psychotherapy has no side effects or medication interactions. Thus, it can be utilised in patients regardless of illness severity, comorbidities, or medication use(Celano et al., 2016).

CBT has been the most-studied psychotherapy in patients with heart disease. To date, nearly all studies examining the use of CBT in cardiac patients have focused on the management of depression, not anxiety disorders (Cully et al., 2010; Gary, Dunbar, Higgins, Musselman & Smith, 2010; Dekker et al., 2011; P. J. Tully, Selkow, Bengel & Rafanelli, 2015; Freedland et al., 2009; Berkman et al., 2003). In patients with CAD (post-MI or post-CABG surgery) or HF, CBT leads to significantly greater improvements in psychological symptoms (typically depression and anxiety) compared to usual care or enhanced usual care (Berkman et al., 2003; Freedland et al., 2009; Freedland, Carney, Rich, Steinmeyer & Rubin, 2015). While these studies targeted patients with depression, they are important because they demonstrate that CBT is feasible in patients with cardiac disease and can lead to improvement in psychological health.

Only one study has examined the impact of CBT for anxiety in patients with cardiovascular disease. This study enrolled 29 patients with comorbid major depression and General anxiety disorder who were participating in a HF self-care program (P. J. Tully, Selkow et al., 2015). Patients chose whether to receive CBT focused on General anxiety disorder or depression, then received CBT focused on that disorder for 12 weeks. Both interventions led to non-significant improvements in depression and anxiety scores, with minimal differences between groups,

though the GAD-focused CBT group had fewer unplanned admissions during the follow-up period than the MDD-focused group (P. J. Tully, Selkow et al., 2015). Limitations of this study include the small sample size, lack of randomisation, and the presence of pharmacologic intervention concurrent with CBT. However, it does suggest that CBT focused on anxiety disorders may be effective.

Pharmacotherapy

Antidepressant medications are the most commonly used pharmacological treatments for a variety of anxiety disorders, including General anxiety disorder, PTSD, and PD. While there is evidence that selective serotonin reuptake inhibitorss (SSRIs), some serotonin-norepinephrine reuptake inhibtors (SNRIs), and tricyclic antidepressantss (TCAs) are effective for the management of General anxiety disorder, PTSD, and PD (Zitrin, Klein & Woerner, 1980; Linehan, Goodstein, Nielsen & Chiles, 1983; Stein & Sareen, 2015). No studies have been conducted to examine their efficacy for treating these disorders in patients with cardiovascular disease. However, these agents have been studied in depressed cardiac patients, providing data on their safety and tolerability in this population.

Again, although anxiety disorders at large and CHD have been at the centre of many important research efforts, the relationship of anxiety disorders and CTR has not received any attention so far.

Chapter 4

Aim of Thesis

Chapter four discusses the aim of this thesis and delineates the research questions which will be addressed in the analysis of the study data.

4.1 Problem statement

As detailed in Chapter three, the psychological (accompanying) reactions to acute and chronic heart diseases are the subject of current research. In a nutshell, there is robust evidence supporting the relevance of psychosocial factors for coronary heart disease, chronic heart failure, arterial hypertension, and some arrhythmias (Albus et al., 2019). Large-scale epidemiological studies have shown that mental illness (Albus et al., 2019; Vaccarino et al., 2019; Cohen et al., 2015), such as PTSD, depression, and anxiety disorders increase the risk of coronary heart disease and worsen the prognosis of affected patients. Furthermore, it has been shown that mental illness almost doubles the risk of (further) heart attacks and, ultimately, mortality (Rutledge, Redwine, Linke & Mills, 2013). To the best of my knowledge, only three studies by Bayer-Topilsky et al. (Bayer-Topilsky et al., 2016, 2015, 2013) have specifically focused on the psychological burden of valvular heart disease in the context of chronic mitral regurgitation to date. In their 2013 study, Bayer-Topilsky et al. endeavoured to define the prevalence and consequences of PTSD as an emotional response to cardiac diseases in patients with chronic mitral regurgitation. For this, they prospectively enrolled 186 patients with moderate or severe organic mitral regurgitation, presenting NYHA class I (absent) or II (minimal) dyspnea and compared them with 80 controls of similar age (38 with completely normal cardiac function; 42 with mild mitral-valve prolapse). They assessed mitral-regurgitation severity as well as PTSD, anxiety, and depression symptoms. However, only patients with no, or at most mild, mitral

regurgitation were included in their study. Bayer-Topilsky et al. were able to show that PTSD prevalence was higher in chronic mitral regurgitation patients than in controls (23% *vs.* 9%, $p < .01$). Although mitral regurgitation objective severity (*regurgitant volume* : 77.8 ± 28.9 *vs.* $79.0 \pm 27.5mL$, $p = .8$) and objective consequences (*left atrial volume* : 59.1 ± 20.9 *vs.* $54.02 \pm 15.6mL$, $p = .1$ *right ventricular systolic pressure* : 34.1 ± 11.4 *vs.* $32.9 \pm 7.2mm\,Hg$, $p = .6$) were similar with and without PTSD (all $p \geq .1$), patients with PTSD displayed more symptoms (class II 74% *vs.* 38%; fatigue 71% *vs.* 38%, both $p < .0001$) and had higher anxiety and depression scores ($p < .0001$). However, Bayer-Topilsky et al. specifically excluded cardiac patients with an ejection fraction $< 50\%$; NYHA class $\geq$III in their effort to clarify the possible association between psychological burden and NYHA class II, a controversial indicator for surgery (Enriquez-Sarano, Nkomo & Michelena, 2009).

In their 2015 study, Bayer-Topilsky et al. were able to show that patients with severe chronic MR showed significant psychological stress (measured by anxiety and post-traumatic stress [PTS]; both $p < 0.01$) and reported decreased physical health-related-QoL ($p < 0.01$) compared to patients who had not undergone a mitral valve operation or normal controls directly after operations but improved over time (Bayer-Topilsky et al., 2015). In 2016, Bayer-Topilsky et al. assessed whether mitral valve prolapse is associated with patients' reported psychological stress (Bayer-Topilsky et al., 2016). For this, they compared 216 patients with mitral valve prolapse to 65 controls without mitral valve prolapse of similar age and sex (age 61 ± 13 years; 63% men) and assessed the patients' psychological burden (anxiety, depression, post-traumatic stress symptoms), health-related quality of life, and perceived severity of illness. Their results indicated that differentiating patients into no/mild vs. moderate/severe chronic mitral regurgitation revealed no differences in psychological burden or mental health-related quality of life between patients with mitral valve prolapse and those without mitral valve prolapse within each subgroup; no/mild mitral regurgitation and moderate/severe mitral regurgitation (all $p \geq .5$). Via multivariate analysis, they revealed that in their sample mitral valve prolapse was not independently associated with psychological burden or health-related quality of life (all $p \geq .4$). In addition, while objective severity of the illness was not related to psychological burden or health-related quality of life (all $p \geq .2$), the patient's perceived severity of illness predicted all psychological burden (all $p < .03$) and quality-of-life outcomes (all $p < .003$).

These are important findings with regard to chronic mitral regurgitation and associated mitral prolapse. However, to date, the psychological burden of cardiac CTR patients in the wake of AMR has been starkly neglected. Despite its poten-

tially devastating effects on affected patients' physical health, the potential psychological effects have yet to be described. Moreover, while traumatic conditions within the spectrum of acute coronary syndrome and potentially traumatic cardiological treatment procedures (e.g., defibrillator implantation) have been at the centre of research efforts, neither the relationship of PTSD, depression, nor anxiety and CTR has received any attention so far.

The objective of the study presented in this thesis was to use well-established quantitative methods to map psychological stress and the prevalence of PTSD after CTR in a predefined population. However, as these questionnaires, although validated, only provide a limited opportunity for patients to express their views and experiences (Haydon, van der Riet & Inder, 2017), a mixed-method approach was chosen to enable this pilot study to capture a more differentiated picture of the CTR patients' situation.

4.2 Research questions and hypotheses

The presented cross-sectional study aimed to address the following research questions: to assess the prevalence of post-traumatic stress disorder, depression, anxiety disorder as well as medication adherence in CTR patients; to compare the Chordae tendineae rupture sample's assessed symptom burden to an age and sex matched myocardial infarction sample; and to examine resilience and risk factors influencing psychological burden. It was hypothesised that (i) the symptom burden of Post-traumatic stress disorder, depression, and anxiety disorders would be elevated. The psychological burden would be comparable to the symptom burden found in myocardial infarction patients. (ii) Good medication adherence would be associated with lower psychological burden. Furthermore, it was estimated that (iii) males, patients with poorer NYHA status, lower educational level, and a more severe degree of mitral regurgitation would present more psychological burden symptoms. The qualitative part of this work examined how CTR patients perceived the CTR event, ensuing coping mechanisms, and changes in health behaviour and world view following the CTR event at an individual level.

Chapter 5

Materials and methods

The following section details the methodological approaches used to assess the CTR case sample and the myocardial infarction control sample. German versions of implemented instruments, the developed interview guideline as well as the study's patient information and consent forms can be found in the appendix.

5.1 Ethical considerations

Prior to implementation, the presented study was approved by the Ethics Committee of the University Hospital Heidelberg (Ethics application no. S-041/2017) and all participants provided their informed written consent. All participants were able to withdraw their consent at any time without fear of any disadvantage to them. The study was conducted in accordance with the Declaration of Helsinki (most recent version: Fortaleza, Brazil, 2013; (Assembly, n.d.).

5.2 Study design and procedure

For this monocentric, non-interventional, cross-sectional study, clinical and psychometric data was systematically collected in two cardiological samples (CTR case study patients and myocardial infarction control study patients) after hospitalisation for a CTR event or myocardial infarction. Only patients who had been treated for CTR or myocardial infarction in the Department of Cardiology, Heidelberg University Hospital, Germany, were asked to participate in this study. The study design for each of the two study sample groups is detailed in Flowchart 5.1 and 5.2 and the samples will be detailed in the following sections.

5.2.1 Study sample

CTR participants

All patients treated for CTR in the Department of Cardiology of the Heidelberg University Hospital, Germany, in the period between January 2013 and July 2017 were prospectively included in the study ($n = 65$). Predefined exclusion criteria where: manifest psychotic disorder, bipolar disorder, and drug addiction, as well as cognitive impairment as well as current severe comorbid physical conditions, for example, cancer, human immunodeficiency virus. Following initial screening, patients who had either died or who were marked as no longer able to give informed consent (cognitive impairment) were excluded from the sample ($n = 11$, 16.9%). Thereafter, all potentially eligible patients ($n = 54$, 83.1%) were contacted via telephone by an experienced researcher (Anna Cranz (AC)). Two patients could not be contacted as the available contact details were no longer correct ($n = 2$, 3.1%).

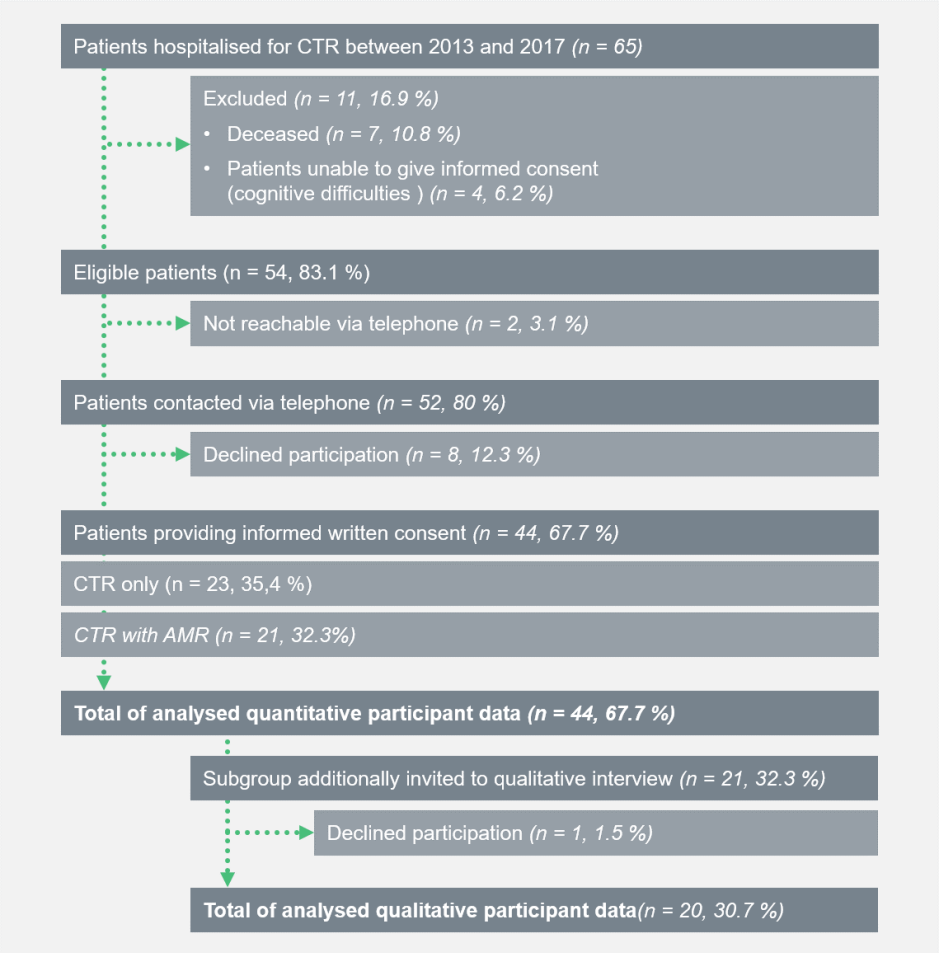

Figure 5.1: Study design flowchart to illustrate the CTR case sample recruitment process

Hence, $n = 52$ CTR patients (80%) were approached and invited to particip-

ate in the study. Of these, eight people ($n = 8$, 12,3%) declined participation. In total, $n = 44$ CTR patients agreed to participate in the study on a voluntary basis and provided their informed written consent (see A.3). All 44 patients who had agreed to participate, completed the quantitative psychometric measures detailed in Section 5.3.3. These psychometric measures could be filled in either during a routine check-up appointment in the Department of Cardiology, Heidelberg University Hospital, Germany, or in the comfort of the patients' homes as restrictions in autonomous mobility must be considered when evaluating patients of this age and frailty. Patients assessed during a routine check-up appointment in the Department of Cardiology, Heidelberg University Hospital, Germany, were met by AC and completed the questionnaires during unavoidable but irksome waiting times in a quiet section of the respective department. Patients choosing to participate in the comfort of their homes scheduled an individual appointment with AC. All patients were able to ask any arising questions during assessment and were able to stop the assessment at any time. After CTR patients had given their written consent, their medical history was screened to differentiate the overall CTR case group into two subgroups according to whether they had been diagnosed with 'CTR only' or had also been diagnosed with 'CTR and subsequent AMR'. Following this screening, the overall sample of CTR patients was divided into two subgroups: the 'CTR only' group comprised 23 patients (35.4%), and the group 'CTR with AMR' comprised 21 participants (32.3%). In addition, a subgroup of 21 (32.3%) patients was invited to participate in a semi-structured interview, the guideline of which is detailed in the section Qualitative measures and can be found in full in the appendix. In total, 20 (30.7%) of these participants agreed to participate in the interview that either took place after the participants had completed the quantitative measures, or during a scheduled appointment with the researcher AC at their home.

Myocardial infarction participants

As the control sample, all patients over the age of 60 who were hospitalised for myocardial infarction and treated on the cardiological ward 'Siebeck' of the Department of Cardiology of the Heidelberg University Hospital, Germany, in the period between January 2016 and July 2018 and were prospectively included in the study ($n = 196$). Predefined exclusion criteria whereas before: manifest psychotic disorder, bipolar disorder, and drug addiction, as well as cognitive impairment as well as current severe comorbid physical conditions, for example, cancer, human immunodeficiency virus. Subsequently, case subjects (CTR patients) were matched with control subjects (myocardial infarction sample) according to age and sex. Following this matching procedure, several control subjects matched each case subject

in terms of sex and age ($n = 96$). In a next step, control cases who had either died or who were not reachable via telephone were excluded ($n = 25$, 26%). In total, 71 patients (74%) were contacted via telephone and invited to participate in the study as controls. For each matched case subject, the researcher contacted potentially eligible control subjects. For example, for an 83-year-old male, the myocardial infarction sample held four control subjects matching his age and gender. In an iterative process, the researcher then contacted the four potential matches to invite them to participate in the study. Once a potential control provided informed consent to participate in the study, the researcher did not contact further matching controls. Following this initial screening process, 27 patients were excluded (28.2%) as they were either no longer able to give informed consent (*cognitive impairment* : $n = 7$, 7.3%) or declined participation ($n = 20$, 28.2%). In total, $n = 44$ myocardial infarction patients agreed to participate in the study on a voluntary basis and either chose to receive the qualitative measures detailed below by post, including a postage paid return envelope and full contact and consent information, or scheduled an appointment with AC. Nine participants were excluded (9.4%), as three failed to include their written consent in the return envelope, while a further two did not return the questionnaires and four questionnaires were excluded due to extensive missing data. Hence, finally, a total of $n = 35$ myocardial infarction controls provided their informed written consent and completed all the quantitative psychometric measures detailed in Section 5.3.3.

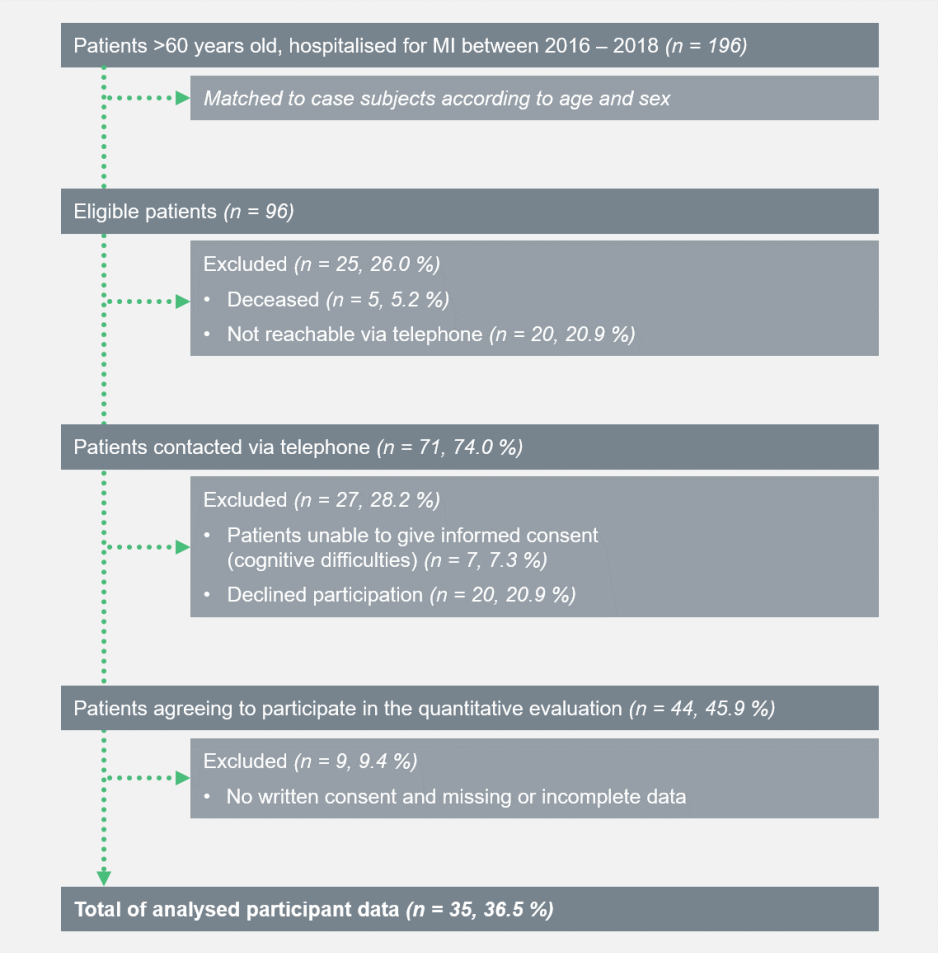

Figure 5.2: Study design flowchart to illustrate the myocardial infarction sample recruitment process

5.3 Study instruments, medical information, and qualitative data

Socio-demographic, medical, psychometric, and qualitative data were collected. Where applicable, established and carefully validated questionnaires were applied to evaluate psychometric parameters.

5.3.1 Patients' socio-demographic characteristics

A demographic questionnaire was used to obtain participant characteristics, such as age, sex, level of education, employment, marital status, previous psychiatric history, namely the history of diagnosed past PTSD, depression, and anxiety disorder, as well as prior and current medication use.

Table 5.1: Normal ranges and severity partition cutoff values for 2DE-derived LVEF

	Normal range	Mildly abnormal	Moderately abnormal	Severely abnormal
	LV EF (%)	LV EF (%)	LV EF (%)	LV EF (%)
Female	52–72	41–51	30–40	<30
Male	54–74	41–53	30–40	<30

5.3.2 Patients' medical characteristics

Patients' medical characteristics were retrieved from their electronic hospital medical files and included their cardiac history (documented previous myocardial infarction or angiographically documented coronary artery stenosis or insufficiency), the presence and type of significant present co-morbid risk factor illnesses, namely diabetes mellitus, obesity, nicotine abuse, and the indexed cardiac event diagnosis (i.e.myocardial infarction, CTR, AMR). Additionally, the following clinical data were collected, where available: left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), 6-Minute walking distance assessed via the Six-Minute Walk Test (6MWT), degree of mitral regurgitation, and NYHA class.

The left ventricular ejection fraction and the left ventricular end-diastolic diameter

To quantify how well the left ventricle is able to pump blood through the body with each heartbeat, left ventricular function measurements are used (Dupuis Marlène et al., 2017). The LVEF is an key parameter in echocardiography as it can alter in several diseases. The LVEF correlates with numerous clinical symptoms, such as the severity of dyspnea, and is an important prognostic factor in acute myocardial infarction. LV systolic dysfunction is defined as an LVEF fraction $< 60\%$ and/or an LVEDD ≥ 45 mm. Severe LV dysfunction is set at a LVEF of $< 30\%$ (Members et al., 2012). The normal range cut-off values of dysfunction are shown in Table 5.1 for males and females (Lang et al., 2015):

The LVEDD indicates LV end diastolic dimension and normal ranges diastolic dimension (mm) are defined as between for males $42.0 - 58.4$ and between $37.8 - 52.2$ for females. It can be used to calculate Fractional Shortening (FS) is a 2D M-Mode method.

The Six-Minute Walk Test

6MWT is used to measure the maximum distance that a person can walk in 6 minutes and is commonly used to assess function in patients with cardiovascular

or pulmonary disease (Steffen, Hacker & Mollinger, 2002). In studies in patients with CHD, lung disease and elderly patients, the 6MWT has be shown to be a valid functional performance test and is accordingly recommended by the European Society of Cardiology (Remme, Swedberg, Task Force for the & Treatment of Chronic Heart Failure, 2001). A distance of less than 300 min 6 minutes predicted an increased likelihood of death among 833 subjects with left ventricular dysfunction (Steffen et al., 2002).

5.3.3 Quantitative measures

The following established psychometric measures were used to evaluate the participants' psychological burden:

The Post-traumatic Diagnostic Scale

Primary traumatisation was assessed by the well-established German version (Griesel, Wessa & Flor, 2006) of the Post-traumatic Stress Diagnostic Scale (Post-traumatic Diagnostic Scale (PDS); (Foa, Cashman, Jaycox & Perry, 1997). The PDS was developed in 1997 by Foa et al. as the first psychometric instrument to map all criteria *A - F* of PTSD from DSM-IV (*A = traumatic experience*, *B = intrusions*, *C = avoidance*, *D = hypervigilance*, *E = time criterion*, *F = functional impairment*; (Foa et al., 1997). It consists of 4 parts: part 1 and 2 evaluate the presence of a traumatic experience, part 3 assesses the intensity of the three main symptoms intrusions, avoidance, hypervigilance as well as the time criterion and part 4 assesses functional impairment in everyday life. The PDS allows for both the dichotomous (PTSD yes/no) and continuous evaluation of data (symptom severity of intrusions, prevention and hypervigilance). Every item is answered on a four point Likert scale ranging from 0 to 3; the severity score ranges from 0 to 51. The German translation of the PDS was validated by Griesel et al. in 2006 (Griesel et al., 2006). The cut-offs for the symptoms severity rating categories are as follows: $< 10 :$ *mild*, > 11 *and* $< 20 :$ *moderate*, > 21 *and* $< 35 :$ *moderate to severe* $> 36 :$ *severe*. In relation to PTSD diagnoses through structured clinical interviews Clinician-Administered PTSD Scale for DSM-5 (CAPS), a sensitivity of 100 % and a specificity of 64% have been shown. The PDS result is evaluated as positive (high probability of PTSD) if at least one positive value is achieved for all symptom criteria *A - F* (Griesel et al., 2006). In the present work, the PDS was applied in an adapted form: the CTR or myocardial infarction event was defined as the A criterion and all DSM-IV criteria *A - F* were reviewed with the focus on the event. Accordingly, the evaluation resulted in a dichotomous parameter (PDS-adap, see

appendix). The procedure is based on Kiphuth et al. approach in their well-known preliminary study on PTSD and transient ischemic attacks (Kiphuth, Utz, Noble, Kohrmann & Schenk, 2014).

The German Dissociative Experience (Fragebogen zu Dissoziativen Symptomen) 20-Item Scale

The questionnaire on dissociative symptoms (German: Fragebogen zu Dissoziativen Symptomen, Questionnaire for Dissociative Symptoms (FDS)) is the authorised German translation and editing of the Dissociative Experiences Scale (Dissociative Experiences Scale (DES); (E. M. Bernstein & Putnam, 1986) by Freyberger (Freyberger et al., 1998; Rodewald, Gast & Emrich, 2006). The DES is the internationally most frequently used and best-validated screening instrument for dissociative disorders (E. M. Bernstein & Putnam, 1986). The DES records everyday dissociative experiences and pathological dissociative symptoms and provides an overall measure of the severity of the dissociative symptoms. Further differential diagnosis is recommended above a certain total value (cut-off). However, there is no generally accepted rule. In the literature rather different cut-off values of 15 - 30 points are mentioned for the DES (cf. e.g.(E. Bernstein et al., 1993; Boon & Draijer, 1993; Steinberg, Rounsaville & Cicchetti, 1991)). The FDS (Freyberger et al., 1998) is a German version of the DES, which was extended by a subscale to conversion symptoms in order to adapt the questionnaire to the ICD-10 classification. In addition, Spitzer et al. (C. Spitzer, Mestel, Klingelhöfer, Gänsicke & Freyberger, 2004) published a 20 item short version of the FDS, the FDS-20, which was extracted from the FDS's 44 item version based on item analysis results. The 20 items with the highest selectivity were extracted from the FDS's original 44 items and combined into the short version FDS-20. On a rating scale ($0 = never$, $100 = always$) divided into 10% steps, the participants estimate how often they have encountered the respective dissociative experience. The mean value is calculated from the frequency estimates as the total score. In addition, subscale values for amnesia, depersonalisation/derealisation, absorption experience and conversion can be calculated. For the evaluation, which requires that no more than two items remain unanswered, the item values are aggregated and then divided by the number of answered items; the calculated mean value can thus fluctuate between 0 and 100. The cut-off values of 13 FDS and 15 points DES, FDS, DES and FDS-20 enable reliable screening for complex dissociative disorders. The FDS, as well as its short form FDS-20, shows similarly good quality criteria as the original version (Freyberger et al., 1998). The internal consistency (Cronbach's α) lies between 0.91 and 0.93, the test-retest reliability between 0.80 and 0.82. Furthermore, there are percentile rank standards for

samples of healthy individuals and various clinical groups.

The Patient Health Questionnaire

The Patient Health Questionnaire (PHQ) was developed as a self-rating instrument by the American psychiatrist Robert L. Spitzer and the internist Kurt Kroenke (C. Spitzer et al., 2004). A German version (PHQ-D) was developed at the Heidelberg University Hospital and its validity has since been proven in numerous studies involving multiple patient groups (Gräfe, Zipfel, Herzog & Löwe, 2004). The PHQ-D covers eight mental disorders that can be divided into two groups: A) Disorders for which the PHQ-D assesses all diagnostic criteria for the specific diagnosis according to DSM-IV ('threshold' disorders) including major depression, panic disorder, and bulimia nervosa. B) disorders for which fewer criteria are requested than are necessary for a specific DSM-IV diagnosis ('subthreshold disorders'). These include the other depressive disorders, other anxiety disorders, somatoform disorders, alcohol abuse, and the binge eating disorder. As the DSM-IV criteria are not completely assessed, these sections have a screening rather than a diagnostic function. Since the PHQ-D directly queries the diagnostic DSM-IV criteria, the instrument has a high content validity. In addition to the diagnostic modules, psychosocial functioning as well as eight frequent psychosocial stressors are also investigated. For this work, established short form of the PHQ-D was used comprising the depression module (9 items), the panic disorder (5 items), and general anxiety disorder module (7 items) as well as one item assessing psychosocial functioning ((Gräfe et al., 2004); (Löwe et al., 2008)). In the following subsections each used module will be presented in more detail.

The Brief PHQ-D's Depression Module

Depressive symptoms were assessed with the German version of the PHQ-9 Depression Module (Gräfe et al., 2004) from the Patient Health Questionnaire [PHQ; (Gräfe et al., 2004)]. The module assesses depressive symptoms, the severity of the disorder, and the development of symptoms according to DSM-IV criteria (Gräfe et al., 2004) and shows very good validity (Kroenke, Spitzer & Williams, 2001). Nine items evaluate whether a patient has experienced depressive symptoms in the past two weeks. The items are scored on a scale from 0 (not at all) to 3 (nearly every day). The severity of depressive symptoms is determined by calculating the sum score ranging between 0 (no depressive symptoms) and 27 (all symptoms occur daily). Scores between 1 and 4 suggest minimal depressive symptoms, scores between 5 and 9 suggest a mild depression, scores between 10 and 14 suggest a moderate

depression, and scores of 15 or above suggest a severe depression (Kroenke et al., 2001). In a representative German norm sample, the mean sum score for depression was $M = 3.60$ ($SD = 4.08$; (Rief, Nanke, Klaiberg & Braehler, 2004).

The Brief PHQ-D's Panic Disorder Module

The PHQ Panic Module consists of 15 questions, each question assessing a DSM-IV criterion of the panic disorder. The Brief PHQ-D's panic disorder scale only comprises five items and has been proven to be suitable for the screening of panic disorders according to the DSM-IV criteria. The scale is evaluated categorically, i.e. (based on the procedure for diagnosing a panic disorder according to DSM-IV) a given number of questions in the module must be answered with "Yes" in order to be able to diagnose a panic syndrome (Gräfe et al., 2004).

The Brief PHQ-D's Generalised Anxiety Disorder Module

The German version (Löwe et al., 2008) from the Patient Health Questionnaire Anxiety Module, the Generalised Anxiety Disorder Scale (GAD-7; (R. L. Spitzer, Kroenke, Williams & Löwe, 2006)), was used to assess symptoms of a generalised anxiety disorder. This questionnaire was designed to assess anxiety symptoms according to DSM-IV criteria over the past two weeks and shows good validity. All seven items are scored on a scale from 0 (not at all) to 3 (nearly every day). The severity of anxiety symptoms is determined by calculating the sum score ranging between 0 (no anxiety symptoms) and 21 (all symptoms occur daily): scores between 1 and 4 suggest minimal anxiety disorder symptoms, scores between 5 and 9 suggest a mild anxiety disorder, scores between 10 and 14 suggest a moderate anxiety disorder, and scores of 15 or above suggest a severe anxiety disorder. In a study with a representative population sample, the mean sum score of the GAD-7 was $M = 2.9$; ($SD = 3.4$; (Löwe et al., 2008)).

The Morisky Medication Adherence Scale

The MMAS is an eight-item questionnaire developed by Morisky et al. to measure drug compliance (Morisky, Ang, Krousel-Wood & Ward, 2008). This scale was initially developed to evaluate medication adherence in patients with hypertension but it is now widely used in various other patient populations. The scale consists of eight questions: the first seven items have a dichotomous answer (yes/no) that indicates adherent or non-adherent behaviour; item 8 assesses how often a patient fails to take their medication via a 5-point Likert scale. A total score of all items is calculated with a sum score ranging from 0 to 8 for adherence. MMAS-8 score can

be calculated if the respondent answered at least 6 of the 8 items. The MMAS scores were trichotomized previously into the following 3 levels of adherence: high adherence (score, 8), medium adherence (score, 6 to < 8), and low adherence (score, < 6). These cut-off values were established based on the association between adherence to medication and blood pressure control in patients with hypertension. The validity was demonstrated with a sample of patients taking antihypertensive drugs by measuring the actual improvement in values. The German version was validated in 2015 by Arnet et al. (Arnet, Metaxas, Walter, Morisky & Hersberger, 2015).

5.3.4 Qualitative measures

All qualitative data was gained during individual, semi-structured interviews conceptualised to last between 10 to 30 minutes on average. The interviewing researcher, AC, is an experienced clinical psychotherapist. A specially developed interview guideline was followed in individual face-to-face settings either in the hospital or at the participants' homes. All interviews were audio-recorded and subsequently verbatim transcribed.

Interview guideline

The interview guideline was developed based on an in-depth literature review, the criteria of the COREQ checklist (Tong, Sainsbury & Craig, 2007), as well as discussions in a team of experts ($N = 3$, all of whom were experienced in qualitative research). The interview manual was constructed in a semi-standardised manner (Helfferich, 2019); (Knox & Burkard, 2009). Key leading questions concentrating on the patient's experiences of the CTR event were developed (see appendix). If necessary, these questions were followed by encouraging and clarifying questions. In line with the 'consolidated criteria for reporting qualitative research'-checklist [COREQ] (Tong et al., 2007), all participants were again informed about the study's background, objectives, and procedure.

Chapter 6

Data analysis

6.1 Quantitative analysis and statistical measures

The data were evaluated using individually generated codes to ensure anonymity. All data were coded and analysed using the software package IBM® SPSS® Statistics (version 24). Descriptive statistics were used to describe the major study variables and sample demographics, raw data are displayed by showing the MD and standard deviation (SD). Stepwise and robust multiple regression models were computed in R (RDevelopment, 2018) to estimate the influence of group (myocardial infarction, CTR only, and CTR with AMR) and socio-demographic variables (sex, age, marital status and educational level) on psychological burden (PTSD, Depression, General anxiety disorder) and medication adherence. For all models, the same blocks of predictive variables were sequentially entered in the following order: (1) socio-demographic information, (2) group variables 'CTR only' and 'CTR with AMR' and always compared with the myocardial infarction group. Intercorrelations among study variables and variance inflation factors (VIF) were assessed to determine multicollinearity.

6.2 Qualitative content analysis

For qualitative analysis, a constructivist thematic analysis approach was implemented. The constructivist approach implies that existing relevant literature, e.g. comparative studies on psychopathology, such as PTSD, depression, anxiety and CHD (Haydon et al., 2017), influences research question development and that the resulting sensitisation primes ensuing data analysis. thematic analysis (TA) is a pragmatic approach to qualitative analysis focusing on the search for identifiable themes across a data set (Braun & Clarke, 2006). Although it draws on some tech-

niques of grounded theory (Kennedy & Lingard, 2006; Strauss & Corbin, 2000), TA follows a six-phase analysis process allowing more flexibility and alleviating adaption to specific study ramifications (Mayring, 2015). After verbatim transcription, open line by line coding of all 20 interviews was conducted to identify recurring topics. Specific sentences (or combinations of sentences) were identified as a code representing the most elemental unit of meaning (Mayring, 2015). The assignment of codes to specific themes was conducted by two independent analysts (Christoph Nikendei (CN) and AC) using the software MaxQDA (2010 version, VERBI GmbH, Berlin), discussed to reach consensus, and adjusted if necessary. Themes were compared and adapted, until overarching relevant themes could be defined. In a final step, themes were summarised into three relevant categories. All codes were analysed for each theme comparing meaning and frequency, and consolidated through a profound expert team discussion. Figure 6.1 illustrates the analysis procedure. Participants' characteristics were managed with the software package IBM® SPSS® Statistics (version 24) and displayed by showing the mean (MD) and standard deviations (SD).

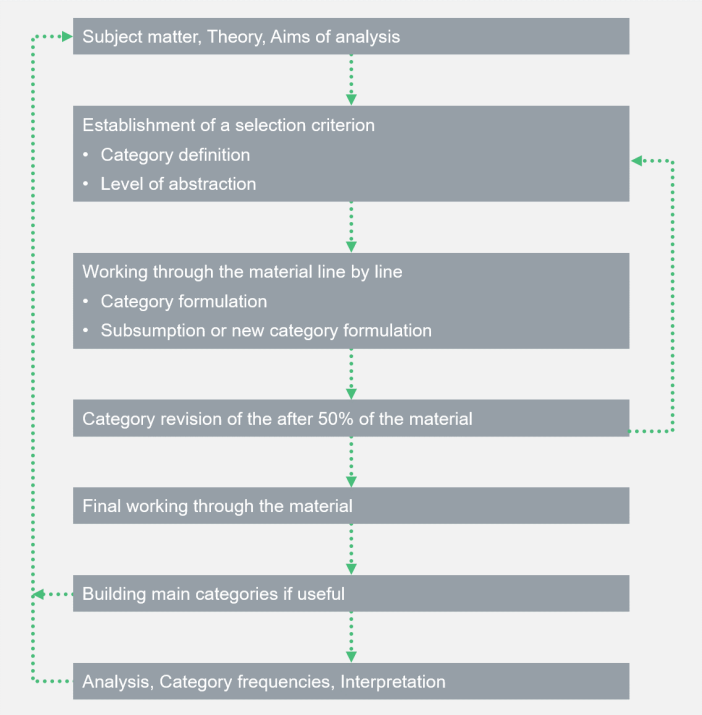

Figure 6.1: The subsequent content analysis followed the principles of Mayring's qualitative content analysis methodology (Mayring, 2015). First, an open coding for all interviews was carried out in order to search for recurring motifs. Single or few contiguous propositions were identified as code representing the most elementary unit of meaning. In the next step, the codes were grouped into relevant categories individually for each interview using the MaxQDA software (2010 version, VERBI GmbH, Berlin).

Chapter 7

Results

7.1 Results of the quantitative evaluation

7.1.1 Sample description

A summary of socio-demographic characteristics and study variables is shown in Table 7.1. The sample's age ranged from 63 to 91, with an average of 81.9 years ($SD = 5.1$) for the overall CTR sample and slightly younger for the myocardial infarction sample with an average of 78.9 years ($SD = 5.1$, range 63 to 89), as reported drop out was largely attributable to old age and female sex. More than half of the overall CTR sample (58.8%) were male (60% for the myocardial infarction sample). 22.7% were widowed without new partner in the overall CTR group and 31% were widowed without new partner in the myocardial infarction sample. Hence, almost 78% of participants reported that they were either in a relationship or married. About 73% of the whole sample had completed at least between 9 to 12 years of school education and were qualified in a trade or craft. 15.2% had completed higher education (university degree) and only 6,3% reported no school qualifications. Overall, 88,8% of the CTR group and 97% of myocardial infarction group reported to have had either PTSD, depression or anxiety disorder in their lifetime prior to this study.

7.1.2 Psychological burden and medication adherence

With regard to the study response variables (PTSD, General anxiety disorder, depression and medication adherence), means and SD are presented in Table 7.1. Analysis of means for PTSD, assessed with the PDS, revealed moderate symptom burden for the overall CTR group ($M = 21.40$, $SD = 12.5$), mild PTSD symptom burden for the group 'CTR without AMR' ($M = 13.74$, $SD = 10.78$) and moderate

to severe symptom burden for the group 'CTR with AMR' ($M = 29.81$, $SD = 6.91$), while the myocardial infarction group also showed moderate PTSD symptom burden ($M = 22.94$, $SD = 4.99$). Across all groups the symptom burden for General anxiety disorder, assessed with the GAD-7, was mild to moderate (overall CTR group: $M = 9.91$, $SD = 4.24$; myocardial infarction group ($M = 8.60$, $SD = 4.91$). Means for depression scores revealed moderate symptom burden across all groups (overall CTR group: $M = 7.84$, $SD = 4.05$; myocardial infarction group ($M = 7.60$, $SD = 4.70$). Overall, medication adherence was good across groups, with the group 'CTR without AMR' yielding the highest means ($M = 6.09$, $SD = 1.44$) and the group myocardial infarction yielding the lowest mean ($M = 4.77$, $SD = 1.82$). With regard to dissociative symptoms, assessed with the FDS-20, means indicated minimal burden for all groups (overall CTR group: $M = 2.95$, $SD = 5.9$; myocardial infarction group ($M = 2.28$, $SD = 5.46$).

Table 7.1: CTR and myocardial infarction patients' socio-demographic characteristics and study variables for PTSD, General anxiety disorder, depression, and medication adherence. CTR patients data are as a whole and as two subgroups: "CTR without AMR" and "CTR with AMR"

	overall CTR[1] n = 44		**CTR[1] without AMR[2] n = 23**		**CTR[1] with AMR[2] n = 21**		**MI[3] n = 35**	
	n (%)	M[11](SD)[12]	n (%)	M[11](SD)[12]	n (%)	M[11](SD)[12]	n (%)	M[11](SD)[12]
Gender								
Male	25 (58.8)		11 (47.8)		14 (66.7)		21 (60.0)	
Female	19 (43.2)		12 (52.2)		7 (33.3)		14 (40)	
Age		81.9 (5.1)		81.6 (5.9)		82.3 (4.2)		78.9 (5.1)
Marital status								
Married	7 (15.9)		3 (13.0)		4 (19)		10 (28.6)	
In a relationship	27 (61.4)		16 (69.6)		11 (52.4)		14 (40.0)	
Widowed	10 (22.7)		4 (17.4)		6 (28.6)		11 (31.4)	
Educational level (scale 1 to 5)		2.7 (1.1)		2.8 (1.2)		2.7 (0.9)		3 (1.2)
Clinical parameters								
LV EF[4]%	28 (63.6)	30.0 (11.9)	10 (43.5)	34.4 (15.1)	18 (85.7)	27.5 (9.2)		
LV EDD[5]	36 (81.8)	59.9 (10.8)	5 (56.5)	57.9 (12.7)	18 (85.7)	61.9 (8.4)		
6 min walking distance [s]	37 (84.1)	346.8 (97.3)	16 (69.6)	342.4 (116.9)	21 (100)	350.2 (82.2)	8 (22.9)	438.5 (131)
Degree of mitral regurgitation	31 (40.5)	3.1 (0.5)	15 (65.2)	3.1 (0.5)	16 (76.2)	3.1 (0.5)	2 (5.7)	2 (1.4)
NYHA[6](scale 1 to 5)	38 (86.4)	2.9 (0.5)	17 (73.9)	2.9 (0.5)	21 (100)	2.8 (0.6)		
Additional diagnoses								
Nicotine	27 (61.4)		13 (56.5)		14 (66.7)		26 (74.3)	
Diabetes	24 (54.5)		14 (60.9)		10 (47.6)		24 (68.6)	
Adipositas	25 (56.8)		14 (60.9)		11 (52.4)		20 (57.1)	
History of treatment for								
Anxiety disorder	15 (34.1)		7 (30.4)		8 (38.1)		13 (37.1)	
Depressive disorder	17 (38.6)		9 (39.1)		8 (38.1)		16 (45.7)	
PTSD[7]	7 (15.9)		4 (17.4)		3 (14.3)		5 (14.3)	
Study response variables								
PTSD[7]		21.40 (12.5)		13.74 (10.78)		29.81 (6.91)		22.94 (4.99)
GAD[8]		9.91 (4.24)		9.91 (4.48)		9.90 (4.08)		8.60 (4.91)
DEP[9]		7.84 (4.05)		8.82 (4.07)		6.76 (3.83)		7.60 (4.70)
MED AD[10]		5.89 (1.51)		6.09 (1.44)		5.67 (1.59)		4.77 (1.82)

[1] Chordae tendineae rupture; [2] acute mitral regurgitation; [3] myocardial infarction; [4] left ventricular ejection fraction; [5] left ventricular end-diastolic diameter; [6] New York Heart Association classifications; [7] Post-traumatic stress disorder; [8] General anxiety disorder; [9] depression; [10] medication adherence; [11] Mean; [12] Standard deviation;

7.1.3 Resilience and risk factors

Stepwise and robust multiple regression models were computed to estimate the influence of group (myocardial infarction, CTR only, and CTR with AMR)

and socio-demographic variables (sex, age, marital status and educational level) on psychological burden (PTSD, Depression, General anxiety disorder) and medication adherence. All regression assumptions were tested for violation with the R-package olsrr (Hebbali, 2018). Inspection revealed no assumption violations for the models with the response variables PTSD, General anxiety disorder and medication adherence. However, for the model with the response variable depression, the assumption of normal distribution was violated ($Shapiro - Wilk = 0.96$, $p = 0.015$; $Anderson - Darling = 0.89$, $p = 0.022$). Hence, results were computed using robust regression analyses by the lm_robust function of the R-package estimate (Graeme Blair & Sonnet, 2019). Colinearity among covariates was assessed using pairwise scatterplots, correlation coefficients and VIF. According to (Kleinbaum, Kupper, Nizam & Rosenberg, 2013), a VIF value greater than 10, and tolerance values less than 0.10 may indicate the presence of multicollinearity. The two measures indicated no sign of multicollinearity between the predictor variables in the present data. The VIF for all predictors was less than 1.28.

The results of the stepwise and robust multiple regression analyses are shown in Table 7.2. In the Model for PTSD, stepwise multiple regression analysis was used to test if groups (myocardial infarction, CTR only, and CTR with AMR) and socio-demographic variables (sex, age, marital status and educational level) significantly predicted participants' PTSD score as compered to myocardial infarction patients. The model explained 44% of the variance ($R^2 = .44$, $F(9, 44) = 6,72$, $p < .001$). However, only two predictors namely group membership in either 'CTR with AMR' or 'CTR only' were significant. Hence, data suggests that CTR patients who had experienced AMR ($\beta = 7.87$, $p < .001$) were more likely to have PTSD as compared to the myocardial infarction group, while patients who had only experienced CTR ($\beta = -8.06$, $p < .001$) were less likely to report PTSD as compared to the myocardial infarction group.

In the Model for General anxiety disorder, stepwise multiple regression analysis was used to test if groups (myocardial infarction, CTR only, and CTR with AMR) and socio-demographic variables (sex, age, marital status and educational level) significantly predicted participants' General anxiety disorder score as compared to myocardial infarction patients. The results of the regression showed no significant findings ($R^2 = 0.07$, $F(0, 97) = 6,72$). Hence, no group differences were found and the General anxiety disorder score could not be predicted by the risk and resilience factors.

In the Model for depression, robust multiple regression analysis was used to test if groups (myocardial infarction, CTR only, and CTR with AMR) and socio-demographic variables (sex, age, marital status and educational level) significantly

predicted participants' depression score as compared to myocardial infarction patients. The model explained 17% of the variance ($R^2 = .17$, $F(2, 80) = 6.72$, $p < .05$). However, only gender turned out to be a significant risk factor ($\beta = 2.75$, $p < .01$). Hence, data indicates that female gender significantly predicted depression across all groups.

In the Model for medication adherence, multiple regression analysis was used to test if groups (myocardial infarction, CTR only, and CTR with AMR) and socio-demographic variables (sex, age, marital status and educational level) significantly predicted participants' medication adherence score as compered to myocardial infarction patients. The model explained 23% of the variance ($R^2 = .23$, $F(3.62) = 6, 72, p < .01$). However, only educational level ($\beta = -.41$, $p < .05$), and 'CTR only' ($\beta = 1.26$, $p < .01$) were significant predictors of medical adherence. Participants with a lower educational level and with CTR only, had a better medical adherence.

Table 7.2: Results of the regression analyses with models for Post-traumatic stress disorder, General anxiety disorder, depression and medication adherence assessing the influence of the groups myocardial infarction, CTRCTR, AMR and socio-demographic variables (sex, age, marital status, and educational level) on psychopathology (PTSD, depression, General anxiety disorder) and medication adherence

	Model for PTSD[1]				**Model for GAD[2]**				**Model for DEP[3]**				**Model for MEDAD[4]**			
	β[5]	se[6]	t[7]	p[8]	β[5]	se[6]	t[7]	p[8]	β[5]	se[6]	t[7]	p[8]	β[5]	se[6]	t[7]	p[8]
Age	-0.32	0.17	-1.86	0.067†	0.09	0.10	0.9	0.368	0.06	0.08	0.91	0.365	-0.03	0.04	-1.01	0.314
Sex	-2.16	1.80	-1.20	0.235	0.90	1.10	0.82	0.411	2.75	1.03	2.67	0.009**	0.63	0.38	1.65	0.103
Marital status	-0.07	1.26	-0.06	0.953	-0.16	0.77	-0.21	0.830	-0.25	0.67	-0.36	0.715	0.37	0.36	-1.01	0.313
Educational level	0.11	0.80	0.14	0.889	0.95	0.48	1.95	0.055†	-0.29	0.40	-0.71	0.477	-0.41	0.17	-2.42	0.018*
CTR only[9]	-8.06	2.07	-3.88	0.000***	1.11	1.26	0.88	0.380	0.64	1.20	0.53	0.594	1.26	0.43	2.88	0.005**
CTR with AMR[10]	7.87	2.16	3.64	0.000***	1.36	1.32	1.04	0.303	-0.99	1.15	-0.85	0.393	0.90	0.45	1.98	0.051†
Model summary																
Model F[11]	F = 9.44***				F = 0.97				F = 2.80*				F = 3.62**			
df[12]	6.72				6.72				6.72				6.72			
(R^2)[13]	0.44				0.07				0.17				0.23			
$(\Delta\ R^2)$[14]	0.39				-0.00				0.10				0.17			

[1] Post-traumatic Stress Disorder; [2] Generalised Anxiety Disorder; [3] Depression;
[4] medication adherence [5] Regression coefficient; [6] Standard error; [7] t-error; [8] $*** = p < .001$, $** = p < .01$, $* = p < .05$, $† = p < 0.1$; [9] Chordae Tendineae Rupture subgroup without acute mitral regurgitation; [10] Chordae Tendineae Rupture subgroup with acute mitral regurgitation (myocardial infarction subgroup = reference group for both subgroups);
[11] Indicator if there is a relationship between the predictors and the response variables ($*** = p < .001$, $** = p < .01$, $* = p < .05$, $† = p < 0.1$); [12] degrees of freedom; [13] explained variance of the response variables by the predictors; [14] adjusted R^2;

Figure 7.1 visualises the model for PTSD that was computed via stepwise multiple regression analysis to test if groups (myocardial infarction, CTR only, and CTR with AMR) and socio-demographic variables (sex, age, marital status and educational level) significantly predicted participants' PTSD score as compered to myocardial infarction patients.

Figure 7.2 shows the box chart comparison of group differences with regard to PTSD scores. The visualised data indicates that the CTR subgroup 'CTR with AMR' reported the highest means 7.1, followed by the myocardial infarction group, while patients in the 'CTR only group' reported the lowest means.

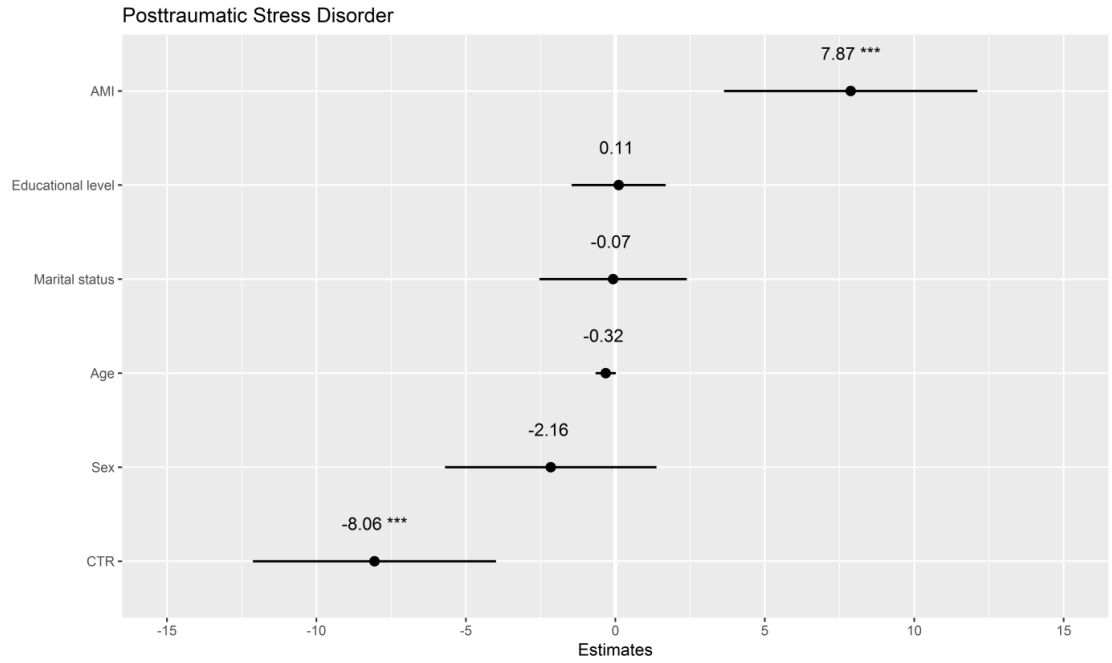

Figure 7.1: Post-traumatic Stress Disorder - Visualised model for variables Chordae Tendineae Rupture subgroup without acute mitral regurgitation (CTR), Chordae Tendineae Rupture subgroup with AMI (myocardial infarction subgroup = reference group for both subgroups), Educational level, Sex, Age and Marital status

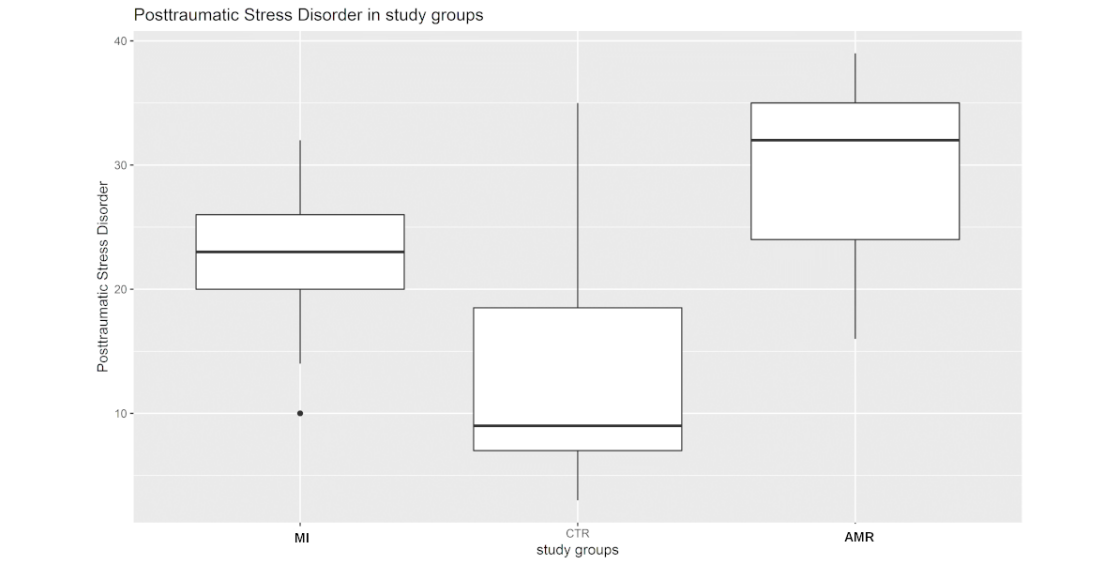

Figure 7.2: Box Chart: comparison of post-traumatic stress disorder means across study groups CTR = Chordae Tendineae Rupture subgroup without acute mitral regurgitation, AMR = Chordae Tendineae Rupture subgroup with acute mitral regurgitation, MI = myocardial infarction group

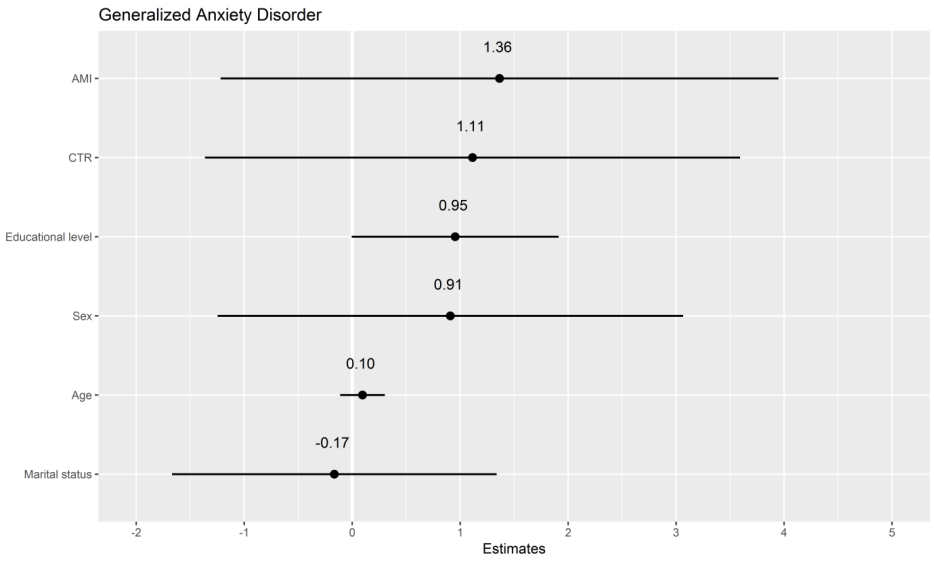

Figure 7.3: Generalised anxiety disorder - Visualised model of variables Chordae Tendineae Rupture subgroup without acute mitral regurgitation (CTR), Chordae Tendineae Rupture subgroup with acute mitral regurgitation (AMI) (myocardial infarction subgroup = reference group for both subgroups), educational level, sex, age and marital status

Figure 7.3 visualises the model for General anxiety disorder that was computed via stepwise multiple regression analysis to test if groups (myocardial infarction, CTR only, and CTR with AMR) and socio-demographic variables (sex, age, marital status and educational level) significantly predicted participants' General anxiety disorder score as compered to myocardial infarction patients.

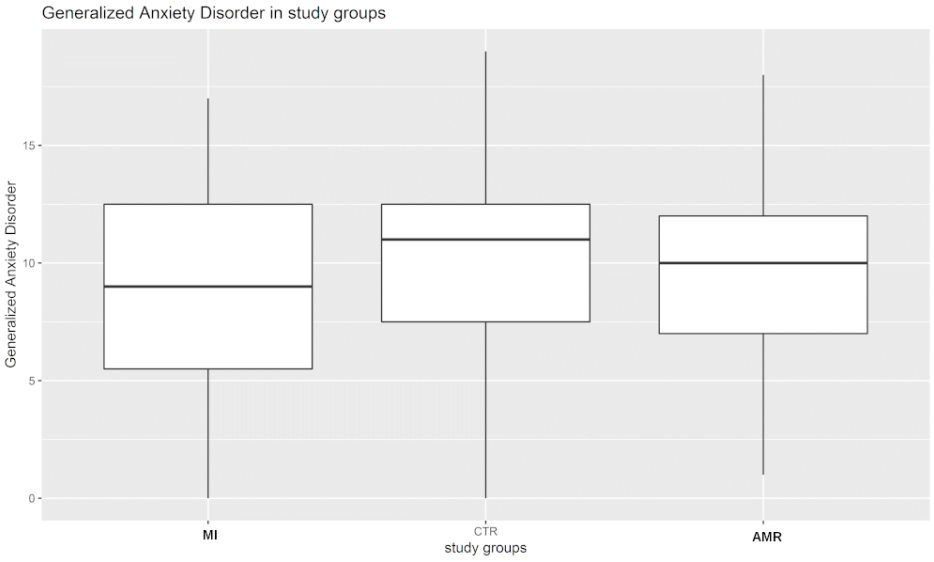

Figure 7.4: Box Chart: comparison of generalised anxiety disorder means across study groups CTR = Chordae Tendineae Rupture subgroup without acute mitral regurgitation, AMR = Chordae Tendineae Rupture subgroup with acute mitral regurgitation, MI = myocardial infarction group

Figure 7.4 shows the box chart comparison of group differences with regard

to General anxiety disorder scores. The visualised data indicates no differences between the groups 7.1.

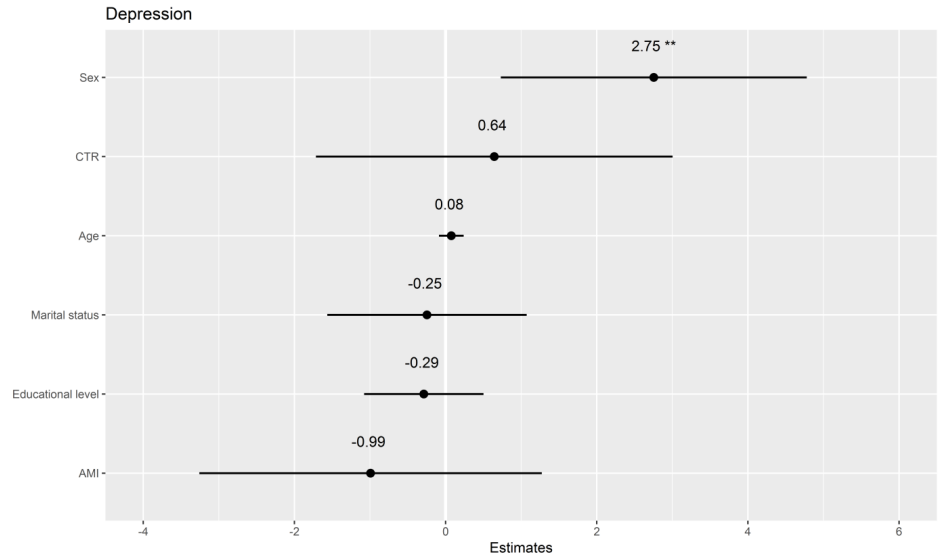

Figure 7.5: Depression - Visualised model of variables Chordae Tendineae Rupture subgroup without acute mitral regurgitation (CTR), Chordae Tendineae Rupture subgroup with acute mitral regurgitation (AMI) (myocardial infarction subgroup = reference group for both subgroups), Educational level, Sex, Age and Marital status

Figure 7.5 visualises the model for depression that was computed via robust multiple regression analysis to test if groups (myocardial infarction, CTR only, and CTR with AMR) and socio-demographic variables (sex, age, marital status and educational level) significantly predicted participants' depression score as compered to myocardial infarction patients.

Figure 7.6 shows the box chart comparison of group differences with regard to depression scores. The visualised data indicates that the CTR subgroup 'CTR only' reported slightly higher means 7.1, while patients in the 'CTR with AMR' and patients in the myocardial infarction group reported similar lower depression means.

Figure 7.7 visualises the model for medication adherence that was computed via stepwise multiple regression analysis to test if groups (myocardial infarction, CTR only, and CTR with AMR) and socio-demographic variables (sex, age, marital status and educational level) significantly predicted participants' medication adherence score as compered to myocardial infarction patients.

Figure 7.8 shows the box chart comparison of group differences with regard to medication adherence scores. The visualised data indicates high means across all study groups, suggesting high perceived medication adherence in all groups. However, patients in the myocardial infarction group reported lower means compared to overall CTR patients 7.1.

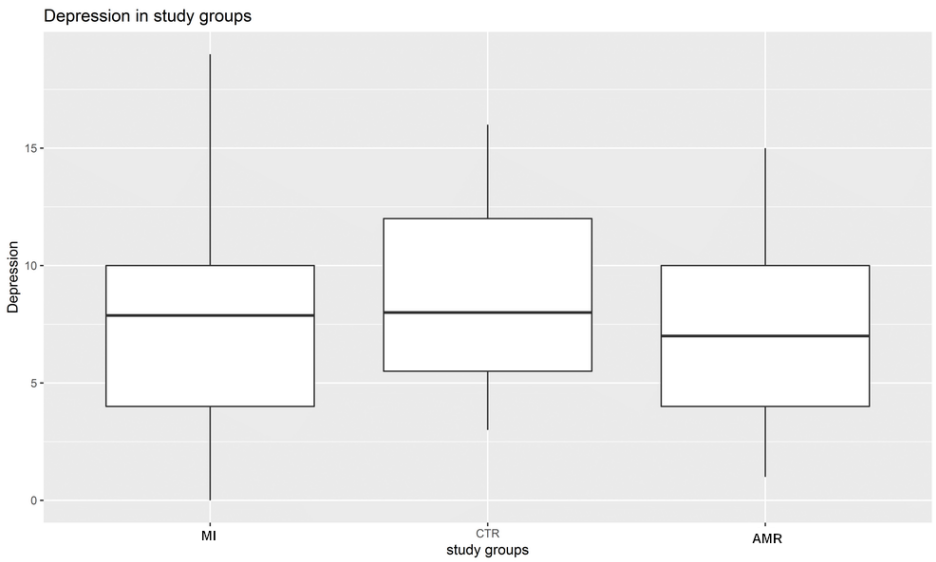

Figure 7.6: Box Chart: comparison of depression means across study groups CTR = Chordae Tendineae Rupture subgroup without acute mitral regurgitation, AMI = Chordae Tendineae Rupture subgroup with acute mitral regurgitation, MI = myocardial infarction group

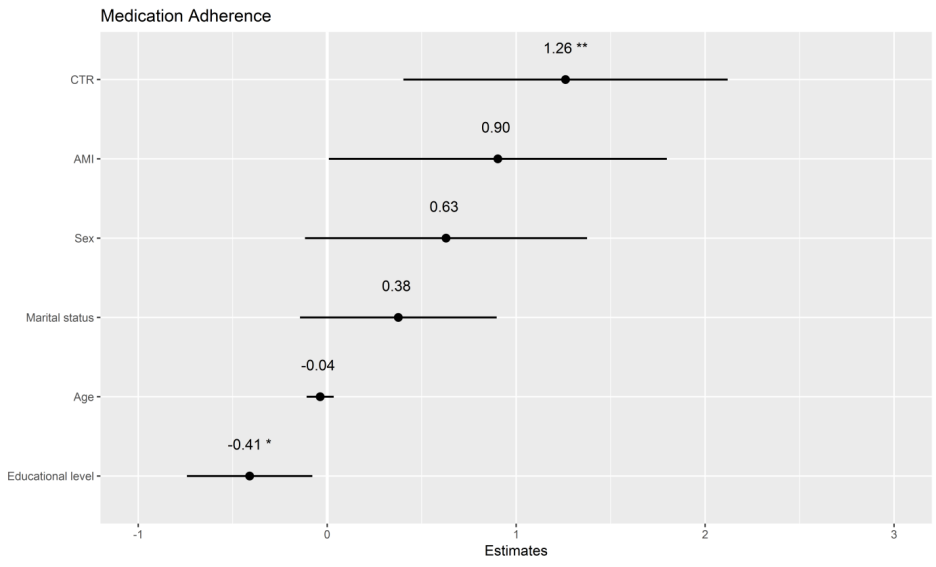

Figure 7.7: Medication Adherence - Visualised model of variables AMR, CTR, Educational level, Sex, Age and Marital status

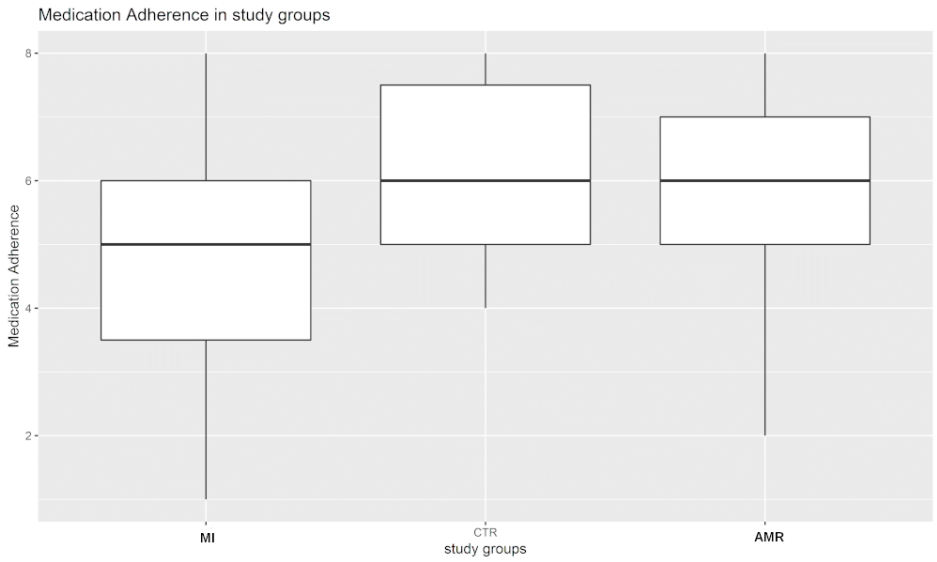

Figure 7.8: Box Chart: comparison of medication adherence means across study groups CTR = Chordae Tendineae Rupture subgroup without acute mitral regurgitation, AMR = Chordae Tendineae Rupture subgroup with acute mitral regurgitation, myocardial infarction =myocardial infarction group

7.2 Results of the qualitative evaluation

In the following section, the results of the qualitative analysis of the 20 semi-structured interviews with CTR patients shall be presented, including an overview of the main categories and themes as well as exemplary quotes to illustrate the description of the themes.

Interviewed participant's characteristics

Twenty participants gave their consent on a voluntary basis to take part in the qualitative section of the study (60% : *male*; *aged* : $81\pm$; SD : 5.9 *years*; *range* : $63-89$). On average, an interview lasted 20.3 minutes ($\pm\, SD$: 8.9; *range* : $10-35\, min$). The length of the interview was adapted to meet individual needs of the interviewees.

Main categories and themes

The qualitative analysis of the interviews identified 1290 single codes, from which three main categories and twelve themes were derived. Figure 7.9 provides an overview of the main categories and themes as defined below for interviewed patient group. The number of codes per category and corresponding theme is shown in parentheses. Illustrative quotations for main categories and themes are listed in Figures 7.10, 7.11 and 7.12.

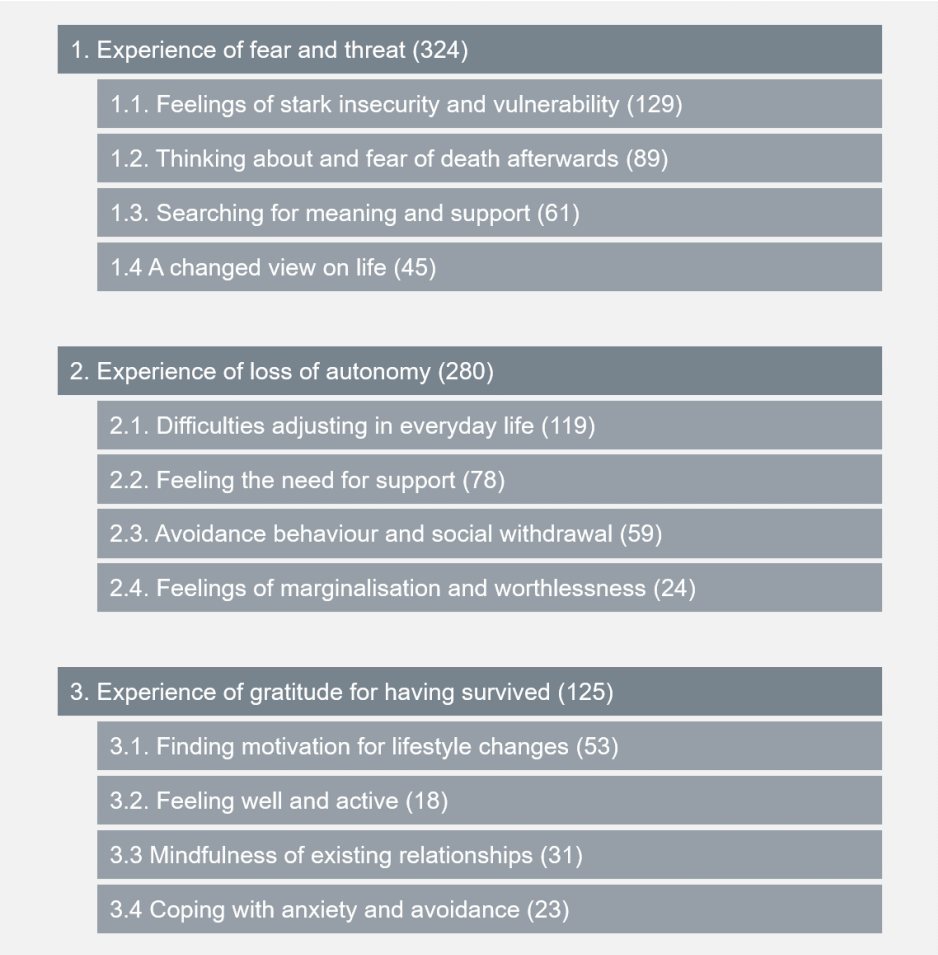

Figure 7.9: Summary of the main categories and themes after qualitative analysis of the CTR patient's experiences as reported during the semi-structured interview

Main category 1: Experience of fear and threat (324 codes)

The experience of fear and the confrontation with death was a prominent point in the participants' narratives. Feeling that they had experienced their own mortality and the finiteness of life, many participants felt fortunate to have survived. Four themes could be differentiated for this main category; exemplary statements are shown in figure 7.10

Theme: 1.1. Feelings of stark insecurity and vulnerability (129 codes)

The CTR patients who had experienced AMR all reported feelings of intense fear of dying and threat during the event. They highlighted their feeling helplessness as well as stressing their perception of being overwhelmed by the situation. Most participants explained that they felt that something was seriously wrong and that they needed immediate medical attention. Several patients thought that they were going to die. Many patients found stark metaphors and similes for their ex-

perience of progressing oedema and breathlessness, describing that they felt like they were drowning outside of water. Others described an intense feeling of loss of control mixed with anxiety. They also reported feeling vulnerable and unstable in the wake of the event to the extent of not feeling secure in their environment or body. Several of them mentioned that they sometimes had reoccurring nightmares of the event or re-experienced the event if they revisited the place where it had happened.

Theme: 1.2. Thinking about and fear of death afterwards (89 codes)

The interviewees reported increased reminiscing about death and fear of dying in the wake of the CTR event. Many reported the need to take appropriate legal measures, such as writing their will and defining their patient disposal statement. Some began sorting their papers and belongings in fear of burdening their relatives in case of their deaths. Others began looking back on their life and evaluating it. All reported feeling that the experience of the CTR event had a major impact on their feeling of longevity. Although they had been conscious of their age, many had not thought a lot about their death. Several patients felt that the event impressed upon them that they were nearing the end of their life and that their time left was limited.

Theme: 1.3. Searching for meaning and support (61 codes)

Several patients sought comfort and support in their families after hospital discharge which often left them a little insecure as they had largely felt well cared for and harboured in a safe environment. Many were preoccupied with finding meaning in the CTR event. Some felt grateful to have been given 'a wake-up call', while others found it hard to understand why they had been so unlucky to have experienced such an ordeal. Most participants said that they felt an increased wish for talking about the event and seeking security in their existing familial relationships.

Theme: 1.4 A changed view on life (45 codes)

Most participants described that the event had changed their view or perception of life and they felt different after the incident. Although experiencing a large amount of mixed emotions including fear and sometimes a feeling of defeat, most felt that they were able to appreciate life more intensely after having feared to lose it. Many reported to be working hard at living a healthier and balanced life, such as exercising, modifying their diets and quitting smoking. However, some participants felt that though they were more mindful in their everyday life, they

had no wish of changing long-standing habits or routines as they felt they had reached such a high age that it was 'enough'.

Figure 7.10: Qualitative analysis of CTR patient's statements: exemplary quotations related to the main category 1 and respective themes. The number of codes per category and corresponding theme is shown in parentheses.

7.2.1 Main category: 2. Experience of loss of autonomy (280 codes)

The experience of new limitations of their body and new challenges in their everyday functionality was also a key issue across all participants' narratives. Four themes emerged following qualitative analysis; exemplary statements are shown in figure 7.11

Theme: 2.1. Difficulties adjusting in everyday life (119 codes)

Many participants found reemerging in everyday life after hospitalisation difficult and frightening. Several participants required additional help and felt an extreme loss of prior independence and autonomy. They described feeling forced to ask their friends and family for more help and support. While they were grateful for assistance, they found it difficult to ask and to be dependent on others. Many reported to feel that their perception of themselves and their body had altered and that they were struggling to adjust to their new limitations, often behaving more cautiously and conservatively than before. Adjusting their lifestyles made many feel anxiety and insecurity on the one hand but also set them new challenges which increased their sense of control. Many reported to have been advised to change their lifestyle with regards to diet, nicotine abuse and exercise regimes. Two interviewees said that they had moved home, while a further two had moved in with their children for additional support.

Theme: 2.2. Feeling the need for support (78 codes)

Several participants reported that they felt an increased need for support and social interaction in the wake of the CTR event. Many sought to reconnect or reaffirm existing relationships and to intensify their contact with friends and family. Many also expressed their need to talk about the event. Though most felt well cared for during hospitalisation, many felt that they would have benefited from further emotional care or even counselling. One participant reported to have felt so burdened by anxiety and recurring scenes of the event that she had sought professional help. Many of the male participants on the other hand felt reluctant to seek professional help for fear of stigmatisation.

Theme: 2.3. Avoidance behaviour and social withdrawal (59 codes)

Beyond adjusting to their new bodily limits, many participants reported to have developed specific avoidance behaviours. Some felt too insecure to even leave the

house without company. Others had bought cell phones or had enrolled in emergency plans that kept them connected to emergency services by the touch of a button. Many reported having given up more active and strenuous activities, such as bike riding or football. Some of the participants described avoiding certain places for fear of being forcibly reminded of the incident. Some showed further signs of social withdrawal and actively avoided larger groups of people outside. They also mentioned withdrawing from social activities and friends for fear of feeling overwhelmed or exhausted on the one hand, or being confronted with their own limitations and frailty on the other hand.

Theme: 2.4. Feelings of marginalisation and worthlessness (24 codes)

Many participants reported feeling treated differently since they were more overtly limited in their physical fitness. Most participants described being belittled during doctor's appointments in busy practises. Others felt ostracised by society, feeling they no longer had a productive role to play which left them with feelings of self-doubt and worthlessness. Many expressed worry that they were burdensome to their families and too ineffective in their everyday lives. Some participants reported having experienced vexation and lesser treatment from younger, more agile people who wanted to show them that they had been hindered in their routines by their slower pace. One participant said that only now had he noticed how young he felt inside because of the discrepancy between his self-perception and his newly limited physical capacities.

7.2.2 Main category: 3. Experience of gratitude for having survived (125 codes)

Participants experienced a multitude of contrasting feelings during the interviews. Though many reported anxiety and fear of dying, they were largely very grateful to have survived. Again, four themes emerged following qualitative analysis; exemplary statements are shown in figure 7.12.

Theme: 3.1. Finding motivation for lifestyle changes (53 codes)

Most participants, who had reported to have good social networks, felt motivated to embrace necessary lifestyle changes in order to be able to enjoy many further years with their family and friends. Though they often stated to have hoped for more improvement of their health with time and, as described previously, found it difficult to adjust to their new limitations in physical capacity, most

Figure 7.11: Qualitative analysis of CTR patient's statements: exemplary quotations related to the main category 2 and respective themes. The number of codes per category and corresponding theme is shown in parentheses.

interviewees were very grateful to have survived the event. Many especially emphasised the importance of taking their medication regularly and as the doctor had prescribed. However, some interviewees felt that they were not willing to undertake great change in their everyday habits as well as amending health risk behaviours as they felt that their time was already too limited to live a lifestyle they did not perceive as joyful or fitting. However, all participants reported to be more mindful of their lifestyle choices since the event.

Theme: 3.2. Feeling well and active (18 codes)

Some participants reported feeling very well and staying quite active since physical recovery from the CTR event. Many had adopted healthier life choices and said to regularly attend specialist exercise groups (e.g. silver gymnast classes and walking groups) or mindfulness meetings. Though most felt that they were not as bodily able and emotionally stable as prior to the CTR event, they felt that they were taking control over the situation and trying to make the best of life.

Theme: 3.3 Mindfulness of existing relationships (31 codes)

Several participants described changes in their social behaviours and habits after the CTR event. Especially two interviewees who had still been working at the time of the event reported to have previously taken their social relationships for granted and to have invested little energy in maintaining friendships or even their marriages. They highlighted to feel a paradigm shift in their priorities after the event. Most participants reported on being more heedful and mindful of their existing relationships, also feeling that their own vulnerability had enabled them to engage in more open and intimate conversations and self-disclosures.

Theme: 3.4 Coping with anxiety and avoidance (23 codes)

After having initially felt profoundly destabilised and discomforted by the event, reporting increased anxiety, social withdrawal, or clinginess, several participants described the feeling of needing to face their fears and 'get on with the rest of their life'. Some of the participants revealed to have fallen in a rather regressive, depressive state. They portrayed how they had been motivated by others or by themselves to take a more progressive stance with regard to their judgement of their physical and emotional abilities. Some reported an experimental, playful approach, especially when engaging with grandchildren. Other reported a more systematic approach of trial and error to extend their subjective boundaries of their functioning in everyday life. Overall, these interviewees expressed that actively

addressing fears and subsequent avoidance behaviour had helped them to regain some confidence in themselves and the world.

Figure 7.12: Qualitative analysis of CTR patient's statements: exemplary quotations related to the main category 3 and respective themes. The number of codes per category and corresponding theme is shown in parentheses.

Chapter 8

Discussion

The cross-sectional study presented in this thesis aimed to use well-established quantitative methods to map psychological stress and the prevalence of Post-traumatic stress disorder after Chordae tendineae rupture in a predefined population in a mixed-method approach. In this chapter, both the quantitative as well as the qualitative results of the data analysis shall be discussed and the limitations of this study will be addressed. At the end of the chapter, a conclusion is drawn and an outlook on possible future research questions is given.

8.1 Quantitative data

The results of the data analysis revealed important findings: as hypothesised, chordae tendineae rupture patients are significantly burdened by post-traumatic stress disorder. Moreover, post-traumatic stress disorder is significantly more prevalent in chordae tendineae rupture patients who had suffered acute mitral regurgitation than in chordae tendineae rupture patients with moderate/severe mitral regurgitation. Most interestingly, chordae tendineae rupture patients who had suffered acute mitral regurgitation showed higher post-traumatic stress disorder scores, nearly reaching the Post-traumatic Diagnostic Scale's cut-off score for severe post-traumatic stress disorder symptoms (> 30), than myocardial infarction controls. Accordingly, higher post-traumatic stress disorder scores were primarily predicted by the group factor 'chordae tendineae rupture with acute mitral regurgitation', ($R^2 = .44$, $F(9,44) = 6,72$, $p < .001$; $\beta = 7.87$, $p < .001$), and accounted for approximately 44% of the variance of post-traumatic stress disorder in the stepwise multiple regression model. The mean scores for depression and anxiety were mild to moderate across all groups. In the robust multiple regression model, depression was predicted by female gender ($R^2 = .17$, $F(2,80) = 6.72$, $p <$

.05; $\beta = 2.75$, $p < .01$) which is in line with current global prevalence distributions but was not predicted by age, educational level, or study groups (myocardial infraction, chordae tendineae rupture only, and chordae tendineae rupture with acute mitral regurgitation). Anxiety score could not be predict based on the multiple regression model variables. There has been ample discussion with regard to the prevalence and symptoms of anxiety disorders in cardiological patients due to the fact that many symptoms of anxiety are difficult to differentiate from typically cardiac symptoms, such as dyspnea. In extent literature and results remain controversial. Future research should address the predictors of anxiety disorders in chordae tendineae rupture patients in a longitudinal design with a larger sample size. Medical adherence was predicted by lower educational level and the group variable 'chordae tendineae rupture only'. These results suggest that lower symptom severity improves medical adherence, while higher educational level decreases it. Clear associations have been established between elderly patients' medication adherence and race, drug and dosage form, number of medications, cost of medications, insurance coverage, and physician-patient communication. However, the findings are inconsistent with regard to the effects of patients' age, sex, socioeconomic status, living arrangement, comorbidities, number of physician visits, and knowledge, attitudes, and beliefs about health and need to be addressed in future study designs. The qualitative analysis of the conducted interviews identified 1290 single codes from which three main categories, namely the experience of fear and threat (324 codes) during the chordae tendineae rupture, the experience of loss of autonomy (280 codes) and the experience of gratitude for having survived (125 codes) in the wake of chordae tendineae rupture with four themes each emerged. Qualitative analysis results elucidated the stark physical and psychological impact on patients who had experienced the chordae tendineae rupture and corroborated the quantitative findings of high post-traumatic stress disorder scores on an individual level but also painted a picture of functional as well as dysfunctional coping strategies. In the following subsections, the results summarised above will be discussed in more detail:

8.1.1 PTSD

The presented study is the first to assess psychological burden in terms of PTSD, depression, and anxiety in Chordae tendineae rupture patients. The results of the data analysis revealed important findings: First, as hypothesised, CTR patients are significantly burdened by Post-traumatic stress disorder. Moreover, PTSD is significantly more prevalent in CTR patients who had suffered AMR than in CTR

patients with moderate/severe mitral regurgitation. Compared to myocardial infarction controls, CTR patients who had suffered AMR also showed higher PTSD scores, nearly reaching the PDS cut-off score for severe PTSD symptoms (> 30). Accordingly, the stepwise multiple regression model for PTSD predicted that 44% of variance could be resolved through CTR patients who had experienced AMR in its wake. However, PTSD could neither be predicted by age or gender, nor by medical adherence. The fact that the severity of somatic symptoms in the assessed patients predicted PTSD-pathology is seemingly in contrast to the findings of Bayer-Topilsky et al. (2013). Although their study was able to show that PTSD is also prevalent in chronic moderate or severe mitral-regurgitation patients, their data suggested that PTSD was not determined by objective mitral-regurgitation severity or consequences (Bayer-Topilsky et al., 2013). Bayer-Topilsky et al. (2013) hypothesised that PTSD is linked to anxiety and depression and to somatic cardiac symptoms, such as dyspnea. However, the difference between PTSD as a comorbitiy with negative prognostic impact and PTSD as cardiac induced disease needs to find strong consideration here. In his comprehensive review, detailed in Chapter 3, Vilchinsky et al. argues that in the case on Cardiac-disease-induced PTSD, thus, when criteria A is the cardiac event itself the severity of cardiac disease is a risk factor (Vilchinsky et al., 2017), This studies data on PTSD corroborates these findings and our results are in line with his suggestion that CDI-PTSD is both conceptually and empirically a valid diagnostic entity. Moreover, apart from the quantitative data, the qualitative interviews with the affected patients impressed upon the interviewer and author of this thesis that the experience of an CTR with ensuing AMR is no walk in the park. The interviewees reported anxiety and fear of death during the CTR and ensuing AMR which clinically matched the emotional turmoil and upheaval experienced by victims of violence. That is, as a clinical psychologist the clinical picture did not differ and some interviewees required stabilisation and help in self regulation during the qualitative interview.

The study aimed to determine the prevalence of PTSD and other emotional comorbidities in patients with CTR and acute mitral regurgitation. Our findings reveal a higher prevalence of PTSD among the patients than in the controls. Notably, while the link between anxiety and CTR has been disputed (Margraf, Ehlers & Roth, 1988), PTSD prevalence in CTR with AMR patients did not differ from the MI control group, indicating that PTSD manifestation is associated with the potentially serious cardiac condition and not with the mere presence of a degenerative mitral lesion. The patients also had slightly higher scores and prevalence of anxiety (not significant), but low depression prevalence similar to the MI controls, indicating that psychological manifestations in mitral-regurgitation patients

differ from other coronary patients who manifest high depression rates. However, CTR patients with PTSD had higher scores and prevalence of depression (not significant), which indicates that psycho-emotional manifestations associated with organic-mitral regurgitation may often occur in combination.

Associations between Somatic Symptoms and PTSD

The severity of mitral regurgitation is characterised by a number of objective measurements directly reflecting the valvular lesion (effective-regurgitant orifice, regurgitant volume) or cardiac and haemodynamic consequences of mitral regurgitation. Symptoms are often considered as equivalent in indicating surgery, whether mild (class II) or severe (class III-IV) (Grigioni et al., 2003). Symptoms are less frequent in mild mitral-regurgitation patients but are inconsistently noted among severe organic mitral-regurgitation patients(Avierinos et al., 2008). While purely cross-sectional, data suggests that the response to severe acute mitral regurgitation is highly psycho-emotional, with strong links among development of PTSD, anxiety, potential cardiac symptoms (such as mild dyspnea or fatigue), and the perception that the cardiac disease is more severe in the assessed qualitative data. This association of psycho-emotional response with the symptomatic response has been observed in patients with cardiac or other conditions such as pulmonary disease(Jenkins, Stanton, Savageau, Denlinger & Klein, 1983), asthma (Smith, Redd, DuHamel, Vickberg & Ricketts, 1999), and cancer (Costa-Requena & Gil, 2010). This study is the first to observe it in CTR patients. One possible explanation is that somatic symptoms may lead to high distress, emotional response, and the perception of being more severely affected by somatic symptoms (Nkomo et al., 2006).

8.1.2 Depression and Anxiety

The mean scores for depression and anxiety reached mild to moderate PHQ-9 cutoff scores across all groups. Depression was significantly predicted by female gender but was not predicted by age, educational level, or study groups which is in line with previous findings. In the robust multiple regression model, depression was predicted by female gender ($R^2 = .17$, $F(2, 80) = 6.72$, $p < .05$; $\beta = 2.75$, $p < .01$) which is in line with current global prevalence distributions but was not predicted by age, educational level, or study groups (myocardial infraction, chordae tendineae rupture only, and chordae tendineae rupture with acute mitral regurgitation). Although CHD mortality rates have declined over the past four decades in western countries, this condition remains responsible for one-third of all deaths

in individuals over age 35. Nearly one-half of all middle-aged men and one-third of middle-aged women in the USA will develop some manifestation of CHD. The 2016 Heart Disease and Stroke Statistics update of the AHA reported that 15.5 million people in the USA have CHD. The reported prevalence increases with age for both women and men. For those US people, the lifetime risk of developing CHD with $\geq$ 2 major risk factors is 37.5% for men and 18.3% for women. CVD disease mortality has been declining in the USA and in regions where economies and health care systems are relatively advanced, but the experience is often quite different around the globe. The studies outlined in the sections above illustrate the increasing evidence base for establishing mental health problems as risk factors for the development and progression of CVD. Though evidence is more consistent for depression and traumatic stress, many studies demonstrate that chronic anxiety and exposure to daily stressors also have a negative impact on cardiovascular health. Guidelines from major societies also reflect the growing recognition of the connection between mental and cardiovascular health. The American Heart Association now officially recognises depression as risk factor for poor prognosis among patients following acute coronary syndromes (Zigmond & Snaith, 1983). In addition, European guidelines identify depression, anxiety, and psychosocial stressors, such as work-related stress or poor social support, as risk factors for incident CVD and adverse outcomes in patients with existing CVD (Davidson, 2010). Anxiety score could not be predict based on the multiple regression model variables. There has been ample discussion with regard to the prevalence and symptoms of anxiety disorders in cardiological patients due to the fact that many symptoms of anxiety are difficult to differentiate from typically cardiac symptoms, such as dyspnea. In extent literature and results remain controversial. Future research should address the predictors of anxiety disorders in chordae tendineae rupture patients in a longitudinal design with a larger sample size. The current prevalence rates of anxiety disorder subtypes in CHD samples were generally 2–3% above population estimates obtained in a North American epidemiological survey utilising the DSM-IV (Hohensinner, Niessner, Huber, Weyand & Wojta, 2011). However, the prevalence rate in this study (with any criteria) was markedly lower than the estimates for specific phobias and social phobias (Hohensinner et al., 2011). The prevalence of any anxiety disorder was 15.52%, though this pooled estimate excluded post-traumatic stress disorder which occurs in approximately 1–4% of myocardial infarction patients (Boscarino, 2008). There are few cardiac studies to compare the anxiety disorder prevalence rate other than that reported in populations receiving implantable-cardioverter defibrillators which is between 11 and 28%(Lindahl, Toss, Siegbahn, Venge & Wallentin, 2000). By contrast to anxiety disorders, a 20%

prevalence of major depression was reported in survivors of myocardial infarction (Magyar-Russell et al., 2011) and 15% prevalence reported in coronary artery bypass graft patients (Roest et al., 2010). Together, the findings suggest that anxiety disorders are equally common as depressive disorders in CHD. Importantly, there was considerable comorbidity between depression and anxiety in up to 50% of CHD patients. Though high comorbidity between depression and anxiety is not surprising, the findings might support several learned societies' recommendations (Pelle et al., 2010; P. J. Tully & Cosh, 2013) to assess mood and anxiety disorders contemporaneously. Celano et al. argue that the methodological characteristics of the studies they reviewed was that DSM-IV diagnoses were associated with significantly lower prevalence of panic disorder, agoraphobia, and GAD(Celano et al., 2016). The apparent reduction in anxiety disorder prevalence among CHD samples was likely associated with the methodological trend to report 'any anxiety disorder' rather than specific anxiety disorder subtypes (Bankier et al., 2008) during the post-DSM-IV period. Likewise, Celano highlights the apparent decrease in anxiety disorder prevalence occurred during a period of increased recognition of depression morbidity and large depression trials (von Känel et al., 2007). Considering the uncertainty surrounding the apparent change in anxiety disorder prevalence in CHD, there is a requisite need for larger epidemiological studies of specific anxiety disorders in CHD patients with the most recent taxonomic nosology delineated in the DSM-V (Drexler, 1997). Such studies will enrich our understanding of anxiety disorder diagnosis in CHD, and in turn, enable additional prognostic MACE studies.

8.1.3 Medication adherence

Medication adherence is a crucial part in the management of chronic diseases. As older adults form a greater proportion of the population with chronic diseases and multiple (co-)morbidities, understanding medication adherence in older adults is important. As detailed at the beginning of this chapter, medical adherence was predicted by lower educational level and the group variable 'chordae tendineae rupture only'. These results suggest that lower symptom severity improves medical adherence, while higher educational level decreases it. Clear associations have been established between elderly patients' medication adherence and ethnicity, drug and dosage form, number of medications, cost of medications, insurance coverage, and physician-patient communication. However, the findings are inconsistent with regard to the effects of patients' age, sex, socioeconomic status, living arrangement, comorbidities, number of physician visits, and knowledge, attitudes, and beliefs

about health and need to be addressed in future study designs(Balkrishnan, 1998). While some factors, such as mental state factors, physical function, age, sex, education level, marital status, lack of medication knowledge, polypharmacy, complex dosing regimen, pillbox usage and poor labelling instructions, had contradictory results on investigation. The reason could be that adherence to medication in this population might be context driven. Therefore, when addressing these factors, clinicians should exercise clinical judgement and propose appropriate solutions to them (Yap, Thirumoorthy & Kwan, 2016). Furthermore, multiple studies regarding patient-doctor relationship have stressed the importance of patients understanding why and what kind of medication they are supposed to take. These findings are corroborated by the patients that were interview as part of the qualitative part of this study narratives. Feelings of dependency and worthlessness as well as being treated in a derogatory manner by care givers was a key theme for CTR patients. Interviewed CTR Patients particularly stressed that feeling respected and purposefully was a key factor in their recovery and coping with the traumatic event as well as their perceived doctor-patient relationship. One patient stated that he mistrusted his new care-giver team, as he found contact with them impersonally and generic, hence he also felt wary of taking the prescribed medicines. Moreover, findings suggest that patients inner illness narratives or bio-psychological models should match or be at least partially consistent with the clinicians explanation of their illness. Beyond the well established factor of relationship and the timing of these explanations are also important (Yap et al., 2016). Recently, studies assessing cognitive functioning in patients with mitral insufficiency were able to show executive impairment in patients prior to MitraClip intervention (Terhoeven et al., 2019). Hence, depressed executive functioning may be a further factor contributing to the studies findings that the patients with objectively higher symptom severity (assessed defined by NYHA class and LVEF) and more sever diagnosis (MI) showed poorer medication as compared to CTR Patients who had not experienced AMR. In line with this studies data, Terhoeven et al. state that age and psychological functioning seem less important for cognitive performance improvements n(Terhoeven et al., 2019).

8.2 Qualitative data

The qualitative part of this work examined how CTR patients perceived the CTR event, ensuing coping mechanisms, and changes in health behaviour and world view following the CTR event at an individual level. The qualitative analysis of the conducted interviews identified 1290 single codes from which three main cat-

egories, namely the experience of fear and threat (324 codes) during the chordae tendineae rupture, the experience of loss of autonomy (280 codes) and the experience of gratitude for having survived (125 codes) in the wake of chordae tendineae rupture with four themes each emerged. Surviving a CTR with resulting AMR creates a whirlpool of emotions, ranging from fear, vulnerability and loneliness to gratitude and joy which is in line with other qualitative findings assessing the trauma of cardiac events (Bremer, Dahlberg & Sandman, 2009; Ketilsdottir, Albertsdottir, Akadottir, Gunnarsdottir & Jonsdottir, 2014) Commonly reported were feelings of loss, a search for meaning and a need to find answers as to why it happened to them and why they survived. Impatience and irritability were common in the beginning when survivors had to adjust to their new situation; they wanted life to be as normal, find a reason and determine their possible contribution to the CA, regardless of the real causes. Thoughts of being a terrible person who deserved this were occasionally verbalised, creating feelings of separation and loneliness (Bremer et al., 2009; Ketilsdottir et al., 2014). Bayer-Tolispy et al. were able to show that PTSD in their study sample was also associated with a more severe perceived illness, despite chronic mitral-regurgitation objective measures being very similar between patients with and without PTSD. This observation is consistent with previous findings showing that subjective perception of the traumatic event is a stronger determinant of PTSD than the actual severity of the trauma(Costa-Requena & Gil, 2010). This pessimistic view of the cardiac condition emphasises the importance of examining the association between PTSD and somatic symptoms. And gives rise for future research endeavour to consider perceived severity of illness in a systematic manner. In sum, the qualitative analysis results elucidated the stark physical and psychological impact on patients who had experienced the chordae tendineae rupture and corroborated the quantitative findings of high post-traumatic stress disorder scores on an individual level but also painted a picture of functional as well as dysfunctional coping strategies. Haydon et al. critically appraise and synthesise the qualitative literature on survivors' experiences of a cardiac arrest in order to identify common themes that can inform clinical pathways and thereby improve survivors' psychological burden, assessed via QoL, in their systematic review and meta-synthesis of over 204 qualitative studies assessing survivors' experiences of a cardiac arrest and CPR (Haydon et al., 2017). Their results revealed five emerging themes: multitude of contrasting feelings; disruption in the continuum of time; new reality and psychological challenges; changed body with new limitations; and confrontation with death. These themes are in line with the findings f this study. Another important factor is the individual ability to adjust to mental and health-related demands. This comprises the ability to cope emotionally

with diseases including adapting and/or maintaining favourable health-related behaviour. Despite high demands, several individuals are able to adequately adjust (high resilience), while others develop maladaptive, disease-promoting behavioural patterns. For example, people with traumatic childhood experiences, chronic stress or mental comorbidities (e.g., depression, anxiety) exhibit more disease-promoting behaviour (Michal, Subic-Wrana & Beutel, 2014). The same holds for people with certain personality characteristics like the "Type D personality" (Denollet & Pedersen, 2008) or chronic hostility (Chida & Steptoe, 2009).

8.2.1 Limitations and future research directions

This study has several limitations that need to be noted. Although all patients treated for Chordae tendineae rupture in the Department of Cardiology of the Heidelberg University Hospital, Germany, in the period between January 2013 and July 2017 were prospectively included in the study ($n = 65$), only 44 out of 65 eligible patient participants consented to participate in the study. This limits findings by potentially biasing the analyses, as the current sample represents a selected group of participants. Furthermore, the study is limited by the small number of participants due to the rare nature of the condition CTR. A further concern lies in the fact that the presented study does not represent a randomised controlled trial, leaving the possibility that effects will not be replicable (Ioannidis, 2005). As the presented study is limited by its small pilot sample size, also the number of predictor variables which could be included in the multiple regression models were limited. In addition, the predictors of the study variables were evaluated within a cross-sectional design. In order to confirm the results, longitudinal research would be necessary. However, the presented data are still important as they over a baseline assessment of psychological burden in CTR using more complex statistical methods. Furthermore, limiting the study's generalisability, it must be assumed that the specific pathology profile of this elderly patient sample is different to the pathology profile of younger chordae tendineae rupture patients, especially with regard to number of diagnosis and resulting variable interference as well as with regard to cognitive functioning and perspective on their personal future outlook. Although specific risk factors, such as nicotine abuse and obesity were assessed, and the patients history was screened for severe comorbid conditions, for example, cancer, human-immunodeficiency virus, overt renal failure, lung disease, previous stroke or any other major neurological disease; history of valve repair or replacement as well as a history of psychological illness and substance abuse, they were not comprehensively assessed in this elderly sample. Further potential influencing factors

need to be addressed in a more comprehensive assessment of socio-demographic, medical and psychological aspects, such as attachment style and personality traits, data in a longitudinal design in a younger larger sample. Lastly, although the qualitative content analysis was performed according to principles of inductive category development and was verified by a second researcher, the examination can be considered to be less generalisable than quantitative approaches due to the subjective nature of qualitative studies. However, with the aim of drawing a more complete picture of this multivariate topic and identifying new research aspects, this methodological approach was specifically chosen to elucidate CTRs patients' perceptions and experiences of the CTRs event. However, the qualitative analysis results elucidated the stark physical and psychological impact on patients who had experienced the chordae tendineae rupture and corroborated the quantitative findings of high post-traumatic stress disorder scores on an individual level but also painted a picture of functional as well as dysfunctional coping strategies. Hence, this potential shortfall, can also be considered as a important strength of the study design in light that this is a pilot study. Protective factors found in extent literature, such as social support and progressive coping strategies, were also relevant in the interviewed patients' narratives. Future research should address these protective factors more comprehensively by including quantitative measures in the study design. Despite its limitations, the study presented at the heart of this thesis was able to shed light on the so far neglected psychological burden of cardiac patients with chordae tendineae rupture and presented results point to the fact that there is indeed a need for considering psychosocial factors in the care of chordae tendineae rupture patients. Especially, with regard to the high prevalence of post-traumatic stress disorder in chordae tendineae rupture patients with acute mitral regurgitation, the presented data suggests the necessity for meaningful interventions to prevent post-traumatic stress disorder after chordae tendineae rupture.

8.2.2 Clinical implications and outlook

The research presented in Chapter three has firmly established that psychosocial factors, such as low socioeconomic status, acute and chronic stress, depression, anxiety, and low social support are associated with an unfavourable prognosis in CHD. The findings presented in this thesis with regard to the psychological burden of cardiac patients with CTR corroborate the need for routine assessment of psychosocial problems and mental comorbidities should be routinely assessed in cardiac patients to initiate targeted diagnostics and treatment. With regard to medication adherence, for all patients, treatment should consider age and gender differences

as well as individual patient preferences to ensure better adherence to the sometime challenging and irksome medication regime. Taking a synoptic view on the research reviewed for this thesis, multimodal treatment concepts should comprise education, physical exercise, motivational counselling, and relaxation training or stress management, as suggested. In cases of mental comorbidities, brief psychosocial interventions by primary care providers or cardiologists, regular psychotherapy and/or medications should be offered. While these interventions have positive effects on psychological symptoms, robust evidence for possible effects on cardiac outcomes is still lacking. For coronary heart disease, chronic heart failure, arterial hypertension, and some arrhythmias, there is robust evidence supporting the relevance of psychosocial factors, pointing to a need for considering them in cardiological care. However, there are still shortcomings in implementing psychosocial treatment, and prognostic effects of psychotherapy and psychotropic drugs remain uncertain. There is a need for enhanced provider education and more treatment trials. As the number of studies finding associations between psychological stressors, Post-traumatic stress disorder, and cardiovascular disease grows, the focus of research has appropriately turned to prevention. In order to identify causal mechanisms that could serve as targets for interventions, further prospective studies with repeated measures of psychological stress, biological factors, and cardiovascular outcomes or surrogate markers of CVD are needed. Ongoing data collection in some of the prospective cohort studies described above should help to establish the pathways linking stress and CVD. With regard to CTR patients, the results of the presented pilot study point to a need for considering psychosocial factors in the care of CTR patients. Especially, in light of the found high prevalence of PTSD in CTR Patients with AMR, the data suggests the need for meaningful preventive interventions to deal with PTSD after CTR. As average life expectancy increases, so do the incidence of chronic diseases and the number of persons receiving longterm drug therapy. Hence, elderly patients' psychological burden in general and elderly CTR patients in particular, as assessed in this study sample, as well as their treatment and noncompliance with medication regiments has the potential for sweeping medical and economic consequences and is likely to become increasingly important in the design of disease-management programs for this population (Balkrishnan, 1998). However, a better understanding of the prevalence of psychological stress after CTR needs to be more comprehensively assessed in larger sample sized and across wider age groups in future research. In a nutshell, the presented findings are in line with Shakespeare's imagery: broken heart strings matter and future research needs to determine what pulls the heart strings in further detail.

Chapter 9

Summary

Chordae tendineae rupture is a potentially life-threatening cardiac event often resulting in acute mitral regurgitation with significant haemodynamic dysfunctions that require immediate medical intervention. However, to date, the psychological burden of cardiac patients with chordae tendineae rupture have been starkly neglected. Despite its potentially devastating effects on affected patients' physical health, the potential psychological effects have yet to be described. Moreover, while traumatic conditions within the spectrum of acute coronary syndrome and potentially traumatic cardiological treatment procedures (e.g., defibrillator implantation) have been at the centre of research efforts, neither the relationship of post-traumatic stress disorder, depression, nor anxiety and chordae tendineae rupture has received any attention so far. Hence, although psycho-emotional comorbidities of heart disease have received much attention, little is known about patients' psychological burden after acute severe mitral regurgitation due to chordae tendineae rupture. This pilot study aimed to assess affected cardiological patients' psychological burden after acute severe mitral regurgitation due to chordae tendineae rupture in a mixed-method approach. For the monocentric, cross-sectional, non-interventional study presented in this thesis clinical and psychometric data was systematically collected in two cardiological samples (chordae tendineae rupture case study patients and myocardial infraction control study patients) after hospitalisation for a chordae tendineae rupture event or myocardial infraction. Only patients who had been treated for chordae tendineae rupture or myocardial infraction in the Department of Cardiology, Heidelberg University Hospital, Germany, were asked to participate in this study on a voluntary basis. The psychological burden (post-traumatic stress symptoms, depression, and anxiety) in cardiac patients with chordae tendineae rupture $n = 44$ chordae tendineae rupture patients (*age* 81.9 ± 5 *years*; 59% *men*, *range* $63 - 91$) and in $n = 35$ myocardial infraction patients (*age* 78.9 ± 5 *years*; 60% *men*, *range* $63 - 89$) was assessed

using validated questionnaires. In addition, semi-structured interviews were conducted with a subgroup of 20 chordae tendineae rupture patients from the case sample and subsequently evaluated by means of qualitative content analysis to provide a more precise picture of psychological stress, individual coping mechanisms, and changes in health behaviour after chordae tendineae rupture. Descriptive statistics were used to describe the major study variables and sample demographics. Stepwise and robust multiple regression models were computed in R to estimate the influence of group (myocardial infraction, chordae tendineae rupture only, and chordae tendineae rupture with acute mitral regurgitation) and socio-demographic variables (sex, age, marital status and educational level) on psychological burden (post-traumatic stress disorder, depression, generalised anxiety disorder) and medication adherence. Intercorrelations among study variables and the variance inflation factor were assessed to determine multicollinearity. The results of the data analysis revealed important findings: as hypothesised, chordae tendineae rupture patients are significantly burdened by post-traumatic stress disorder. Moreover, post-traumatic stress disorder is significantly more prevalent in chordae tendineae rupture patients who had suffered acute mitral regurgitation than in chordae tendineae rupture patients with moderate/severe mitral regurgitation. Most interestingly, chordae tendineae rupture patients who had suffered acute mitral regurgitation showed higher post-traumatic stress disorder scores, nearly reaching the Post-traumatic Diagnostic Scale's cut-off score for severe post-traumatic stress disorder symptoms (> 30), than myocardial infraction controls. Accordingly, higher post-traumatic stress disorder scores were primarily predicted by the group factor 'chordae tendineae rupture with acute mitral regurgitation', ($R^2 = .44$, $F(9, 44) = 6,72$, $p < .001$; $\beta = 7.87$, $p < .001$), and accounted for approximately 44% of the variance of post-traumatic stress disorder in the stepwise multiple regression model. The mean scores for depression and anxiety were mild to moderate across all groups. In the robust multiple regression model, depression was predicted by female gender ($R^2 = .17$, $F(2, 80) = 6.72$, $p < .05$; $\beta = 2.75$, $p < .01$) which is in line with current global prevalence distributions but was not predicted by age, educational level, or study groups (myocardial infraction, chordae tendineae rupture only, and chordae tendineae rupture with acute mitral regurgitation). Anxiety score could not be predict based on the multiple regression model variables. There has been ample discussion with regard to the prevalence and symptoms of anxiety disorders in cardiological patients due to the fact that many symptoms of anxiety are difficult to differentiate from typically cardiac symptoms, such as dyspnoea. In extent literature and results remain controversial. Future research should address the predictors of anxiety disorders in chordae tendineae

rupture patients in a longitudinal design with a larger sample size. Medical adherence was predicted by lower educational level and the group variable 'chordae tendineae rupture only'. These results suggest that lower symptom severity improves medical adherence, while higher educational level decreases it. Clear associations have been established between elderly patients' medication adherence and race, drug and dosage form, number of medications, cost of medications, insurance coverage, and physician-patient communication. However, the findings are inconsistent with regard to the effects of patients' age, sex, socioeconomic status, living arrangement, comorbidities, number of physician visits, and knowledge, attitudes, and beliefs about health and need to be addressed in future study designs. The qualitative analysis of the conducted interviews identified 1290 single codes from which three main categories, namely the experience of fear and threat (324 codes) during the chordae tendineae rupture, the experience of loss of autonomy (280 codes) and the experience of gratitude for having survived (125 codes) in the wake of chordae tendineae rupture with four themes each emerged. Qualitative analysis results elucidated the stark physical and psychological impact on patients who had experienced the chordae tendineae rupture and corroborated the quantitative findings of high post-traumatic stress disorder scores on an individual level but also painted a picture of functional as well as dysfunctional coping strategies. Protective factors found in extent literature, such as social support and progressive coping strategies, were also relevant in the interviewed patients' narratives. Future research should address these protective factors more comprehensively by including quantitative measures in the study design. The presented study is limited by its small pilot sample size which also limited the number of predictor variable which could be included in the multiple regression models. Furthermore, limiting generalisability, it must be assumed that the specific pathology profile of this elderly sample is different to the pathology profile of younger chordae tendineae rupture patients, especially with regard to number of diagnosis and resulting variable interference. Further potential influencing factors need to be addressed in a more comprehensive assessment of socio-demographic, medical and psychological data, such as attachment style and personality traits in a longitudinal design in a younger larger sample. Nevertheless, the study presented at the heart of this thesis was able to shed light on the so far neglected psychological burden of cardiac patients with chordae tendineae rupture and presented results point to the fact that there is indeed a need for considering psychosocial factors in the care of chordae tendineae rupture patients. Especially, with regard to the high prevalence of post-traumatic stress disorder in chordae tendineae rupture patients with acute mitral regurgitation, the presented data suggests the necessity for meaningful interven-

tions to prevent post-traumatic stress disorder after chordae tendineae rupture. In a nutshell, presented data are in line with Shakespeare's imagery: broken heart strings matter and future research needs to determine what pulls the heart strings in further detail.

9.1 Zusammenfassung

Die Chordae Tendineae Ruptur ist ein potenziell lebensbedrohliches Herzereignis, das oft zu einer akuten Mitralinsuffizienz mit erheblichen hämodynamischen Dysfunktionen führt, die eine sofortige medizinische Intervention erfordern. Bislang wurde jedoch der psychischen Belastung von kardialen Patienten mit Ruptur der Chordae tendineae und akuter Mitralinsuffizienz nur wenig Beachtung geschenkt. Trotz der potenziell verheerenden Auswirkungen auf die körperliche Gesundheit der betroffenen Patienten, gibt es noch keine Untersuchungen zu den psychologischen Auswirkungen. Während traumatische Zustände im Spektrum des akuten Koronarsyndroms und potenziell als traumatisch erlebte kardiologische Behandlungsverfahren (z.B. Defibrillatorimplantation) im Mittelpunkt der Forschungsanstrengungen standen, wurde die Beziehung zwischen Ruptur der Chordae tendineae sowie Posttraumatischen Belastungsstörungen, Depression oder Angst bisher nicht erforscht. Untersuchungen, welche spezifisch die psychischen Belastungen in Folge einer Ruptur der Chordae tendineae fokussieren, stehen somit noch aus. Die Erkenntnis, ob die Posttraumatische Belastungsstörung eine relevante Komplikation der Ruptur der Chordae tendineae darstellt, ist besonders im Hinblick auf sekundärpräventive Maßnahmen bedeutend. Ziel dieser Pilotstudie war es, die psychische Belastung von betroffenen Patienten nach einer akuten schweren Mitralinsuffizienz durch Chordae Tendineae Ruptur, Resilienzfaktoren und Änderungen des Gesundheitsverhaltens in einem Mixed-Method-Ansatz zu untersuchen. Neben quantitativen psychometrischen Fragebögen wurden semistrukturierte Interviews durchgeführt und mittels qualitativer Inhaltsanalyse ausgewertet. Ein besseres Verständnis der Prävalenz von psychischen Belastungen nach einem Sehnenfadenabriss, mit besonderem Fokus auf die Prävalenz von Posttraumatische Belastungsstörungen, ist bedeutend für die Entwicklung präventiver Interventionen zur Verhinderung einer PTBS nach Ruptur der Chordae tendineae. In der vorgestellten Untersuchung wurden die psychische Belastung bei Herzpatienten mit Sehnenruptur (Posttraumatische Stresssymptome, Depressionen, Angststörungen und Medikamenteneinnahme) unter Verwendung validierter psychometrischer Fragebögen bei $n = 44$ Patienten mit Sehnenfadenabriss (*Alter* $81,9 \pm 5$ *Jahre*; 59% *Männer*, *Bereich* 63 *bis* 91) und bei $n = 35$ Patienten mit Myokard Infarkt (*Alter* $78,9 \pm 5$ *Jahre*; 60% *Männer*,

Bereich 63 *bis* 89) erhoben. Darüber hinaus wurden mit einer Untergruppe von 20 Patienten mit Sehnenfadenabriss Patienten teilstrukturierte Interviews durchgeführt und anschließend mittels qualitativer Inhaltsanalyse ausgewertet, um ein genaueres Bild von psychischem Stress, individuellen Bewältigungsmechanismen und Veränderungen im Gesundheitsverhalten nach dem Sehnenfadenabriss zu erhalten. Deskriptive Statistiken wurden verwendet, um die Belastungsfaktoren und die demographische Stichprobe zu beschreiben. Die Rohdaten werden durch die Darstellung des Mittelwerts (MD) und der Standardabweichungen (SD) angezeigt. Schrittweise und robuste multiple Regressionsmodelle wurden in R berechnet, um den Einfluss der Gruppe (‚Myokardinfraktion', ‚nur Chordae Tendineae Ruptur' und ‚Chordae Tendineae Ruptur mit akuter Mitralinsuffizienz') und soziodemographischer Variablen (Geschlecht, Alter, Familienstand und Bildungsniveau) auf die psychische Belastung (Posttraumatische Belastungsstörung, Depression, Generalisierte Angststörung) und Medikamente Adhärenz abzuschätzen. Interkorrelationen zwischen den Untersuchungsvariablen wurden mittels Varianz-Inflationsfaktor untersucht, um auf Multikollinearität zu prüfen. Die Datenanalyse zeigte, dass Chordae Tendineae Ruptur Patienten signifikant durch posttraumatische Belastungssymptome beeinträchtigt sind. Darüber hinaus ist die Posttraumatische Belastungsstörung bei Chordae Tendineae Ruptur-Patienten, die eine akute Mitralinsuffizienz erlitten haben, signifikant häufiger als bei Chordae Tendineae Ruptur-Patienten mit mittlerer/schwerer Mitralinsuffizienz. Interessanterweise zeigten Chordae Tendineae Ruptur-Patienten, die an akuter Mitralinsuffizienz gelitten hatten, höhere Werte für posttraumatische Belastungsstörungen und erreichten fast den Cut-off-Score der Posttraumatischen Diagnoseskala für schwere posttraumatische Belastungsstörungssymptome (> 30) als Myokardinfraktionskontrollen. Dementsprechend wurden höhere posttraumatische Belastungsstörungswerte in erster Linie durch den Gruppenfaktor "Chordae tendineae ruptur with acute mitral regurgitation" vorhergesagt ($R^2 = .44$, $F(9, 44) = 6,72$, $p < .001$; $\beta = 7,87$, $p < .001$) und machten etwa 44% der Varianz der posttraumatischen Belastungsstörung im schrittweisen multiplen Regressionsmodell aus. Die Durchschnittswerte für Depressionen und Angstzustände waren in allen Gruppen leicht bis moderat. Im robusten multiplen Regressionsmodell wurde Depression nach weiblichem Geschlecht vorhergesagt ($R^2 = .17$, $F(2, 80) = 6,72$, $p < .05$; $\beta = 2,75$, $p < .01$), aber nicht von Alter, Bildungsniveau oder Studiengruppen (‚Myokardinfraktion', ‚nur Chordae Tendineae Ruptur' und ‚Chordae Tendineae Ruptur mit akuter Mitralinsuffizienz') vorhergesagt wurde. Der Angstwert konnte auf der Grundlage der Variablen des Mehrfach-Regressionsmodells nicht vorhergesagt werden. Über die Prävalenz und Symptome von Angststörungen bei kardiologischen Patienten wird viel disku-

tiert, da viele Angstsymptome schwer von typischen kardialen Symptomen, wie z.B. Dyspnoe, zu unterscheiden sind. Zukünftige Forschungen sollten sich mit den Prädiktoren von Angststörungen bei Chordae Tendineae Ruptur Patienten in einem longitudinalen Design mit einer größeren Stichprobengröße befassen. Die Adhärenz wurde durch ein niedrigeres Bildungsniveau und die Gruppenvariable "nur Chordae tendineae ruptur" vorhergesagt. Diese Ergebnisse deuten darauf hin, dass ein geringerer Schweregrad der Symptome die Adhärenz verbessert, während ein höheres Bildungsniveau sie verringert. Es wurden klare Zusammenhänge zwischen der Einhaltung der Medikamente bei älteren Patienten und ihrer ethnischen Herkunft, der Medikamenten- und Dosierungsform, der Anzahl der Medikamente, den Medikamentenkosten, dem Versicherungsschutz und der Kommunikation zwischen Arzt und Patient festgestellt. Die Ergebnisse sind jedoch inkonsistent in Bezug auf die Auswirkungen von Alter, Geschlecht, sozioökonomischem Status, Lebensweise, Komorbiditäten, Anzahl der Arztbesuche sowie Wissen, Einstellungen und Überzeugungen über Gesundheit und müssen in zukünftigen Studiendesigns berücksichtigt werden. Die qualitative Analyse der durchgeführten Interviews identifizierte 1290 Einzelcodes, aus denen drei Hauptkategorien, nämlich die Erfahrung von Angst und Bedrohung (324 Codes) während des Sehenfadenabrisses, die Erfahrung des Verlustes der Autonomie (280 Codes) und die Erfahrung der Dankbarkeit für das Überleben (125 Codes) nach dem Chordae Tendineae Bruchsprung mit jeweils vier Unterthemen entstanden sind. Qualitative Analyseergebnisse verdeutlichten die starken physischen und psychischen Auswirkungen auf Patienten, die die Chordae-Sehnenruptur erlebt hatten, und bestätigten die quantitativen Ergebnisse hoher posttraumatischer Belastungswerte auf individueller Ebene, zeichneten aber auch ein Bild von funktionellen und dysfunktionalen Bewältigungsstrategien. Schutz-faktoren, wie soziale Unterstützung und progressive Bewältigungsstrategien, waren auch in den Erzählungen der befragten Patienten relevant. Zukünftige Forschung sollte diese Schutzfaktoren durch die Einbeziehung quantitativer Maßnahmen in das Studiendesign umfassender behandeln. Die vorgestellte Studie ist durch ihren geringen Stichprobenumfang begrenzt, der auch die Anzahl der Prädiktorvariablen begrenzt, die in die multiplen Regressionsmodelle einbezogen werden konnten. Darüber hinaus ist von einer Einschränkung der Verallgemeinerbarkeit auszugehen, da sich das spezifische Pathologieprofil dieser älteren Probe vom Pathologieprofil jüngerer Chordae Tendineae Ruptur-Patienten wahrscheinlich unterscheidet, insbesondere in Bezug auf die Anzahl der Diagnosen und die daraus resultierenden möglichen Interferenzen. Weitere potenzielle Einflussfaktoren müssen in einer umfassenderen Bewertung soziodemographischer, medizinischer und psychologischer Daten, wie

z.B. Bindungsstil und Persönlichkeitsmerkmale, in einer Längsschnittstudie mit einer jüngeren größeren Stichprobe berücksichtigt werden. Dennoch konnte die in dieser Arbeit vorgestellte Studie Aufschluss über die bisher vernachlässigte psychische Belastung von Herzpatienten mit Chordae Tendineae Ruptur geben und die präsentierten Ergebnisse deuten darauf hin, dass es notwendig ist, psychosoziale Faktoren bei der Versorgung von Chordae Tendineae Ruptur Patienten zu berücksichtigen. Insbesondere im Hinblick auf die hohe Prävalenz posttraumatischer Belastungsstörungen bei Chordae Tendineae Ruptur Patienten mit akuter Mitralinsuffizienz deuten die vorliegenden Daten auf die Notwendigkeit sinnvoller Interventionen hin, um posttraumatische Belastungsstörungen nach Chordae Tendineae Ruptur zu verhindern.

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Part II

Appendix

Appendix A

Forms

A.1 Psychometric questionaires

A.1.1 PDS-ADAP

PDS-ADAP

Bitte kreuzen Sie für die folgenden Fragen JA oder NEIN an:

Während des Sehnenfadenabrisses ...

JA	**NEIN**	... fühlten Sie sich hilflos?
JA	**NEIN**	... hatten Sie starke Angst oder waren Sie voller Entsetzen?
JA	**NEIN**	... dachten Sie, dass Ihr Leben in Gefahr war?
JA	**NEIN**	... wurden Sie körperlich verletzt?

Im Folgenden finden Sie eine Reihe von Problemen, die Menschen manchmal nach belastenden Erlebnissen haben. Bitte lesen Sie sich jedes der Probleme sorgfältig durch. Wählen Sie diejenige Antwortmöglichkeit (0 - 3) aus, die am besten beschreibt, wie häufig Sie **IM LETZTEN MONAT** von diesem Problem betroffen waren. **Die Fragen sollten Sie dabei auf das Erlebnis des Sehnenfadenabrisses beziehen.**

Dabei bedeutet
0 = überhaupt nicht oder nur einmal im letzten Monat
1 = einmal pro Woche oder seltener / manchmal
2 = 2 bis 4 Mal pro Woche / die Hälfte der Zeit
3 = 5 Mal oder öfter pro Woche / fast immer

Hatten Sie belastende Gedanken oder Erinnerungen an das Erlebnis, die ungewollt auftraten und Ihnen durch den Kopf gingen, obwohl Sie nicht daran denken wollten?	0	1	2	3
Hatten Sie schlechte Träume oder Alpträume über das Erlebnis?	0	1	2	3
War es, als würden Sie das Ereignis plötzlich noch einmal durchleben, oder handelten oder fühlten Sie so, als würde es wieder passieren?	0	1	2	3
Belastete es Sie, wenn Sie an das Erlebnis erinnert wurden (fühlten Sie sich z.B. ängstlich, ärgerlich, traurig, schuldig usw.)?	0	1	2	3
Hatten Sie körperliche Reaktionen (z.B. Schweißausbruch oder Herzklopfen), wenn Sie an das Erlebnis erinnert wurden?	0	1	2	3
Haben Sie sich bemüht, nicht an das Erlebnis zu denken, nicht	0	1	2	3

darüber zu reden oder damit verbundene Gefühle zu unterdrücken?				
Haben Sie sich bemüht, Aktivitäten, Menschen oder Orte zu meiden, die Sie an das Erlebnis erinnern?	0	1	2	3
Konnten/ können Sie sich an einen wichtigen Bestandteil des Erlebnisses nicht erinnern?	0	1	2	3
Hatten Sie deutlich weniger Interesse an Aktivitäten, die vor dem Erlebnis für Sie wichtig waren, oder haben Sie sie deutlich seltener unternommen?	0	1	2	3
Fühlten Sie sich Menschen Ihrer Umgebung gegenüber entfremdet oder isoliert?	0	1	2	3
Fühlten Sie sich abgestumpft oder taub (z.B. nicht weinen können oder sich unfähig fühlen, liebevolle Gefühle zu erleben)	0	1	2	3
Hatten Sie das Gefühl, dass sich Ihre Zukunftspläne und Hoffnungen nicht erfüllen werden (z.B. dass Sie im Beruf keinen Erfolg haben, nie heiraten, keine Kinder haben oder kein langes Leben haben werden)?	0	1	2	3
Hatten Sie Schwierigkeiten, ein- oder durchzuschlafen?	0	1	2	3
Waren Sie reizbar oder hatten Sie Wutausbrüche?	0	1	2	3
Hatten Sie Schwierigkeiten, sich zu konzentrieren (z.B. während eines Gespräches in Gedanken abschweifen; beim Ansehen einer Fernsehsendung den Faden verlieren; vergessen, was Sie gerade gelesen haben)?	0	1	2	3
Waren Sie übermäßig wachsam (z.B. nachprüfen, wer in ihrer Nähe ist; sich unwohl fühlen, wenn Sie mit dem Rücken zur Tür sitzen; usw.).	0	1	2	3
Waren Sie nervös oder schreckhaft (z.B. wenn jemand hinter Ihnen geht).	0	1	2	3

Wie lange haben Sie schon die Probleme, die Sie in der obigen Tabelle angegeben haben? (bitte **eine** Antwortmöglichkeit ankreuzen):

- □ weniger als einen Monat
- □ 1 bis 3 Monate
- □ über 3 Monate

Bitte geben Sie an, ob Sie die Probleme, die Sie in der obigen Tabelle angegeben haben, **IM LETZTEN MONAT** in den unten aufgeführten Bereichen Ihres Lebens beeinträchtigt haben. Bitte kreuzen Sie **JA** an, wenn eine Beeinträchtigung vorlag, und **NEIN**, wenn dies nicht der Fall war.

JA	**NEIN**	Arbeit
JA	**NEIN**	Hausarbeit und Haushaltspflichten
JA	**NEIN**	Beziehungen zu Freunden
JA	**NEIN**	Unterhaltung und Freizeitaktivitäten
JA	**NEIN**	(Hoch-)Schule/ Ausbildung
JA	**NEIN**	Beziehungen zur Familienmitgliedern
JA	**NEIN**	Erotik
JA	**NEIN**	Allgemeine Lebenszufriedenheit
JA	**NEIN**	Allgemeine Leistungsfähigkeit in allen Lebensbereichen

FDS-20

Dieser Fragebogen besteht aus 20 Fragen über Erfahrungen und Erlebnisse, die Sie möglicherweise aus Ihrem alltäglichen Leben kennen. Wir sind daran interessiert zu erfahren, in welchem Ausmaß Sie derartige Erlebnisse in den letzten zwei Wochen gehabt haben. Bitte lassen Sie bei Ihren Antworten Episoden unberücksichtigt, in denen Sie unter dem Einfluss von Alkohol, Drogen oder Medikamenten gestanden haben.
Um die Fragen zu beantworten, klicken Sie bitte auf diejenige Prozentzahl, die zeigt, wie oft Ihnen so etwas passiert. 0 % bedeutet niemals und 100 % immer.

1. **Einige Menschen haben zeitweise das Gefühl, dass ihr Körper oder ein Teil ihres Körpers nicht zu ihnen gehört. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

2. **Einige Menschen haben manchmal das Gefühl, als betrachteten sie die Welt durch einen Schleier, so dass Personen und Gegenstände weit entfernt, undeutlich oder unwirklich erscheinen. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

3. **Einige Menschen erleben gelegentlich, dass sie in den Spiegel schauen und sich nicht erkennen. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

4. **Einige Menschen machen manchmal die Erfahrung, neben sich zu stehen oder sich selbst zu beobachten, wie sie etwas tun, und dabei sehen sie sich selbst tatsächlich so, als ob sie eine andere Person betrachteten. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie)

5. **Einige Menschen sind sich gelegentlich nicht sicher, ob Ereignisse, an die sie sich erinnern, wirklich geschehen sind oder ob sie diese lediglich geträumt haben. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

6. **Einige Menschen stellen manchmal fest, dass sie Dinge getan haben, an die sie sich nicht erinnern können. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

7. **Einige Menschen stellen zeitweise fest, dass sie sich so sehr in eine Phantasiegeschichte oder einen Tagtraum hineinversetzen, dass sie den Eindruck haben, diese geschähen wirklich. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

8. **Einige Menschen stellen manchmal fest, dass sie bestimmte Stimmen in ihrem Kopf hören, die sie anweisen, Dinge zu tun, oder die ihr Handeln kommentieren. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

9. **Einige Menschen spüren manchmal Körperteile nicht mehr oder erleben eigenartige Gefühle wie z. B. Brennen, Kribbeln oder Taubheit, ohne dass ein Arzt eine körperliche Ursache finden konnte. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

10. **Einige Menschen stellen gelegentlich fest, dass ihre Beine oder Arme sehr schwach sind oder sie ihre Gliedmaßen gar nicht mehr bewegen können, ohne dass ein Arzt eine körperliche Ursache finden konnte. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

11. **Einigen Menschen passiert es gelegentlich, dass man ihnen vorwirft zu lügen, obwohl sie selbst der festen Überzeugung sind, nicht gelogen zu haben. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

12. **Einigen Menschen passiert es gelegentlich, dass sie ihre Bewegungen nicht mehr koordinieren und kontrollieren können (z. B. greifen sie daneben), ohne dass ein Arzt eine körperliche Ursache finden konnte. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

13. **Einige Menschen haben zuweilen das Gefühl, dass andere Personen, Gegenstände und die Welt um sie herum nicht wirklich sind. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.**

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

14. Einige Menschen erleben gelegentlich, dass sie sich nicht erinnern können, ob sie etwas wirklich getan haben oder lediglich darüber nachgedacht haben, es zu tun (z. B. wissen sie nicht, ob sie einen Brief wirklich eingeworfen haben oder lediglich darüber nachgedacht haben, ihn einzuwerfen). Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

15. Einigen Menschen passiert es zuweilen, dass sie stunden- oder tagelang fast völlig bewegungslos dasitzen, fast nicht sprechen, sich fast nicht bewegen und auch auf äußere Reize, wie z. B. laute Geräusche, nicht richtig reagieren. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

16. Einige Menschen erinnern sich manchmal so lebhaft an ein vergangenes Ereignis, dass sie das Gefühl haben, dieses Ereignis erneut zu erleben. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

17. Einige Menschen stellen manchmal fest, dass sie einfach dasitzen und ins Leere starren, an nichts denken und nicht bemerken, wie die Zeit vergeht. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

18. Einige Menschen erleben gelegentlich, wie sie beim Stehen oder Gehen unsicher werden, eigenartige Bewegungen machen oder sich plötzlich gar nicht mehr bewegen können, ohne dass ein Arzt eine körperliche Ursache finden konnte. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

19. Einige Menschen stellen manchmal fest, an einem vertrauten Ort zu sein und ihn dennoch als fremd und unbekannt zu erleben. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

20. Einige Menschen stellen gelegentlich fest, dass sie in vergleichbaren Situationen so unterschiedlich handeln, dass sie das Gefühl haben, zwei unterschiedliche Personen zu sein. Kennzeichnen Sie bitte mit Ihrer Antwort, wie häufig Ihnen dies passiert.

0 % 10 20 30 40 50 60 70 80 90 100 %
(nie) (immer)

A.1.3 Kurzform PHQ-D

Kurzform PHQ-D				
A) Wie oft fühlten Sie sich im Verlauf der <u>letzten 2 Wochen</u> durch die folgenden Beschwerden beeinträchtigt?	überhaupt nicht	an einzelnen Tagen	an mehr als der Hälfte der Tage	beinahe jeden Tag
1. Wenig Interesse oder Freude an Ihren Tätigkeiten	☐	☐	☐	☐
2. Niedergeschlagenheit, Schwermut oder Hoffnungslosigkeit	☐	☐	☐	☐
3. Schwierigkeiten, ein- oder durchzuschlafen, oder vermehrter Schlaf	☐	☐	☐	☐
4. Müdigkeit oder Gefühl, keine Energie zu haben	☐	☐	☐	☐
5. Verminderter Appetit oder übermäßiges Bedürfnis zu essen	☐	☐	☐	☐
6. Schlechte Meinung von sich selbst; Gefühl, ein Versager zu sein oder die Familie enttäuscht zu haben	☐	☐	☐	☐
7. Schwierigkeiten, sich auf etwas zu konzentrieren, z.B. beim Zeitung lesen oder Fernsehen	☐	☐	☐	☐
8. Waren Ihre Bewegungen oder Ihre Sprache so verlangsamt, dass es auch anderen auffallen würde? Oder waren Sie im Gegenteil „zappelig" oder ruhelos und hatten dadurch einen stärkeren Bewegungsdrang als sonst?	☐	☐	☐	☐
9. Gedanken, dass Sie lieber tot wären oder sich Leid zufügen möchten	☐	☐	☐	☐

B) Fragen zum Thema „Angst"	**JA**	**NEIN**
1. Hatten Sie in den letzten 4 Wochen eine Angstattacke (plötzliches Gefühl der Furcht oder Panik)?	☐	☐
Wenn „NEIN", gehen Sie bitte weiter zu Frage C.		
2. Ist dies bereits früher einmal vorgekommen?	☐	☐
3. Treten manche dieser Anfälle völlig unerwartet auf – d. h. in Situationen, in denen Sie nicht damit rechnen, dass Sie angespannt oder beunruhigt reagieren?	☐	☐
5. Empfinden Sie diese Anfälle als stark beeinträchtigend und/oder haben Sie Angst vor erneuten Anfällen?	☐	☐
6. Litten Sie während Ihres letzten schlimmen Angstanfalls unter Kurzatmigkeit, Schwitzen, Herzrasen oder -klopfen, Schwindel oder dem Gefühl, der Ohnmacht nahe zu sein, Kribbeln oder Taubheitsgefühlen, Übelkeit oder Magenbeschwerden?	☐	☐

A.1.4 GAD-7

C) Wenn eines oder mehrere der in diesem Fragebogen beschriebenen Probleme bei Ihnen vorliegen, geben Sie bitte an, wie sehr diese Probleme es Ihnen erschwert haben, Ihre Arbeit zu tun, Ihren Haushalt zu regeln oder mit anderen Menschen zurecht zu kommen:

Überhaupt nicht erschwert	Etwas erschwert	Relativ stark erschwert	Sehr stark erschwert
☐	☐	☐	☐

GAD-7

Wie oft fühlen Sie sich im Verlauf der <u>letzten 2 Wochen</u> durch die folgenden Beschwerden beeinträchtigt?

	Überhaupt nicht	An einzelnen Tagen	An mehr als der Hälfte der Tage	Beinahe jeden Tag
1. Nervosität, Ängstlichkeit oder Anspannung	☐	☐	☐	☐
2. Nicht in der Lage sein, Sorgen zu stoppen oder zu kontrollieren	☐	☐	☐	☐
3. Übermäßige Sorgen bezüglich verschiedener Angelegenheiten	☐	☐	☐	☐
4. Schwierigkeiten zu entspannen	☐	☐	☐	☐
5. Rastlosigkeit, so dass Stillsitzen schwer fällt	☐	☐	☐	☐
6. Schnelle Verärgerung oder Gereiztheit	☐	☐	☐	☐
7. Gefühl der Angst, so als würde etwas schlimmes passieren	☐	☐	☐	☐

A.1.5 MORISKY

MORISKY		
Vergessen Sie manchmal, Ihre Medikamente einzunehmen?	□ Ja	□ Nein
Manchmal wird ein Medikament nicht genommen, und zwar aus einem anderen Grund, als Vergesslichkeit. Wenn Sie an die letzten 2 Wochen denken, gab es Tage, an denen Sie Ihre Medikamente nicht genommen haben?	□ Ja	□ Nein
Haben Sie jemals die Einnahme Ihrer Medikamente verringert oder gestoppt, ohne Ihren Arzt/Ihre Ärztin zu informieren, weil Sie sich nach der Einnahme schlechter fühlten?	□ Ja	□ Nein
Wenn Sie reisen oder Ihr Zuhause verlassen, vergessen Sie manchmal Ihre Medikamente mitzunehmen?	□ Ja	□ Nein
Haben Sie Ihre Medikamente gestern genommen?	□ Ja	□ Nein
Wenn Sie das Gefühl haben, dass Ihre Erkrankung unter Kontrolle ist, hören Sie manchmal mit der Einnahme Ihrer Medikamente auf?	□ Ja	□ Nein
Jeden Tag Medikamente zu nehmen, empfinden viele Personen als lästig. Fühlen Sie sich manchmal schikaniert, wenn Sie den Therapieplan genauestens einhalten müssen?	□ Ja	□ Nein

Wie oft haben Sie Mühe, sich an die Einnahme aller Ihrer Medikamente zu erinnern?	Immer	Fast immer	Manchmal	Kaum	Nie
	□	□	□	□	□

A.2 Interview guideline

Wie haben Sie den Sehnenfadenabriss erlebt?	
Was ist Ihre Überzeugung, wie es zu dem Sehnenfadenabriss kam?	
Welche Auswirkungen hat Sehnenfadenabriss auf Sie gehabt?	• Körperliche Auswirkungen • Körperwahrnehmung, Vertrauen in den eigenen Körper • Stimmung / Ängstlichkeit • Reizbarkeit / Wachsamkeit • Auswirkungen auf tägliche Aktivitäten (Beruf, Freizeit) • Auswirkungen auf das soziale Umfeld und enge Beziehungen
Wie sind Sie mit diesen Auswirkungen umgegangen?	• Was ist Ihnen dabei schwer gefallen? • Was hat Ihnen geholfen?
Haben Sie seit dem Sehnenfadenabriss etwas an Ihrem Gesundheitsverhalten geändert?	• Was haben Sie geändert? • Wie leicht oder schwer war das für Sie? • Was hat Ihnen dabei geholfen?
Wie kommen Sie mit der Medikamenteneinnahme zurecht?	• Sehen Sie einen Sinn in der Medikamenteneinnahme? • Was bereitet Ihnen Schwierigkeiten bei der Medikamenteneinnahme, was hilft?
Haben Sie Sorge vor einem weiteren schwierigen Krankheitsverlauf?	• Wie gehen Sie mit diesen Sorgen um?
Haben sich seit dem Sehnenfadenabriss Ihre persönlichen Einstellungen in Bezug auf das eigene Leben und die eigene Gesundheit geändert?	

A.3 Consent forms

A.3.1 Consent chordae tendineae rupture version 1

UniversitätsKlinikum Heidelberg

„Psychische Belastung - nach Ruptur der Chordae tendineae““

Einverständniserklärung Studienteilnehmer/in

Ich, _____, erkläre mich hiermit bereit, an der Studie **„Psychische Belastung nach Ruptur der Chordae tendineae.“** teilzunehmen. Über die Inhalte der Studie bin ich ausreichend durch die Informationsschrift, die ich erhalten habe, informiert und zusätzlich mündlich aufgeklärt worden.

Freiwilligkeit

Die Teilnahme an der Studie ist freiwillig. Ich kann mein Einverständnis jederzeit, ohne Angabe von Gründen und ohne für mich entstehende Nachteile, zurückziehen. Frau **Dipl. Psych. Anna Cranz** stand mir hierbei für Rückfragen zur Verfügung.

Unbeantwortete Fragen Sollten Sie Fragen haben, wenden Sie sich bitte an den Projektverantwortlichen.

Projektverantwortlicher

Apl. Prof. Dr. med. Christoph Nikendei, MME

Christoph.Nikendei@med.uni-heidelberg.de

Oberarzt
Universitätsklinikum Heidelberg
Klinik für Allgemeine Innere Medizin und Psychosomatik
am Universitätsklinikum Heidelberg

Thibautstr. 4
69115 Heidelberg

Gemäß § 4 Bundesdatenschutzgesetz (BDSG): "Ich wurde darüber aufgeklärt und stimme zu, dass meine in der Studie erhobenen Daten in pseudonymisierter Form aufgezeichnet (und ggf. auch in pseudonymisierter Form weitergegeben) werden können. Dritte erhalten jedoch keinen Einblick in personenbezogene Unterlagen. Bei der Veröffentlichung von Ergebnissen der Studie wird mein Name ebenfalls nicht genannt."

Im Falle eines Rücktritts

☐ Ja, ich bin damit einverstanden, dass - im Falle eines Rücktritts - die bisher erhobenen Daten meiner Person ausgewertet werden.

☐ Nein, ich möchte nicht, dass die bisher erhobenen Daten von meiner Person ausgewertet werden/wird. Es soll sämtliches Material, das mit meiner Person in Zusammenhang steht vernichtet werden

_____ _____
Ort, Datum Unterschrift des Studienteilnehmers

_____
Unterschrift des Aufklärenden

Ihr persönlicher Code:

Unter „Pseudonymisierung“ versteht man die Verarbeitung personenbezogener Daten in einer Weise, dass die personenbezogenen Daten ohne Hinzuziehung zusätzlicher Informationen („Schlüssel“) nicht mehr einer spezifischen betroffenen Person zugeordnet werden können. Diese zusätzlichen Informationen werden dabei gesondert aufbewahrt und unterliegen technischen und organisatorischen Maßnahmen, die gewährleisten, dass die personenbezogenen Daten nicht einer identifizierten oder identifizierbaren natürlichen Person zugewiesen werden.

Um ein Code für Sie zu generieren, mit dem Ihre Daten wie oben beschrieben pseudonymisiert gespeichert werden können, bitten wir Sie noch, folgende Angaben zu machen:

Notieren Sie unten nacheinander
- den **zweiten** Buchstaben des Vornamens Ihrer Mutter (z.B. „A“ für Sabine)
- den **dritten** Buchstaben des Vornamens Ihres Vaters (z.B. „R“ für Herbert)
- die Summe ihrer **Hausnummer** als zweistellige Zahl (z.B. „09“ für Hausnr. 18)
- die **ersten beiden Buchstaben** des Ortes Ihrer Einschulung (z.B. „Fr“ für Frankfurt).

Zweiter Buchstabe d. Vornamens d. Mutter **z.B. „A“**	Dritter Buchstabe d. Vornamens d. Vaters **z.B. „R“**	Die Summe Ihrer Hausnr. **z.B. „09“**	Ersten beiden Buchstaben des Ortes der Einschulung **z.B. „FR“**

UniversitätsKlinikum Heidelberg

„Psychische Belastung von kardiologischen Patienten nach Ruptur der Chordae tendineae““

Einverständniserklärung Studienteilnehmer/in

Ich habe die Informationsschrift gelesen und wurde zudem mündlich durch **Frau Dipl. Psych. Anna Cranz** über das Ziel und den Ablauf der Studie sowie über die Risiken ausführlich und verständlich aufgeklärt. Im Rahmen des Aufklärungsgesprächs hatte ich die Gelegenheit, Fragen zu stellen. Alle meine Fragen wurden zu meiner Zufriedenheit beantwortet. Ich stimme der Teilnahme an der Studie freiwillig zu. Für meine Entscheidung hatte ich ausreichend Zeit. Ein Exemplar der Informationsschrift und der Einwilligungserklärung habe ich erhalten.

Datenschutz

Mir ist bekannt, dass bei dieser Studie personenbezogene Daten verarbeitet werden sollen. Die Verarbeitung der Daten erfolgt nach gesetzlichen Bestimmungen und setzt **gemäß Art. 6 Abs. 1 lit. a der Datenschutz-Grundverordnung** folgende Einwilligungserklärung voraus:

Ich wurde darüber aufgeklärt und stimme freiwillig zu, dass meine in der Studie erhobenen Daten, insbesondere Angaben über meine Gesundheit[1], zu den in der Informationsschrift beschriebenen Zwecken in pseudonymisierter Form aufgezeichnet, ausgewertet werden können. Dritte erhalten keinen Einblick in personenbezogene Unterlagen. Bei der Veröffentlichung von Ergebnissen der Studie wird mein Name ebenfalls nicht genannt. Die personenbezogenen Daten werden anonymisiert, sobald dies nach dem Forschungszweck möglich ist. Die Daten werden nach Studienabschluss zehn Jahre aufbewahrt und anschließend vernichtet. Mir ist bekannt, dass diese Einwilligung jederzeit schriftlich oder mündlich ohne Angabe von Gründen widerrufen werden kann, ohne dass mir dadurch Nachteile entstehen. Die Rechtmäßigkeit der bis zum Widerruf erfolgten Datenverarbeitung wird davon nicht berührt. In diesem Fall kann ich entscheiden**, ob die von mir erhobenen Daten gelöscht werden sollen oder weiterhin für die Zwecke der Studie verwendet werden dürfen.**

Gemäß § 4 Bundesdatenschutzgesetz (BDSG): "Ich wurde darüber aufgeklärt und stimme zu, dass meine in der Studie erhobenen Daten in pseudonymisierter Form aufgezeichnet (und ggf. auch in pseudonymisierter Form weitergegeben) werden können. Dritte erhalten jedoch keinen Einblick in personenbezogene Unterlagen. Bei der Veröffentlichung von Ergebnissen der Studie wird mein Name ebenfalls nicht genannt."

[1] Gemäß Art. 9 Abs. 1 DSGVO handelt es sich bei Gesundheitsdaten um personenbezogene Daten besonderer Kategorie in deren Verarbeitung der Studienteilnehmer ausdrücklich einwilligen muss. Gleiches gilt für Daten, aus denen die rassische und ethnische Herkunft, politische Meinungen, religiöse oder weltanschauliche Überzeugungen oder die Gewerkschaftszugehörigkeit hervorgehen, sowie für die Verarbeitung von genetischen Daten, biometrischen Daten zur eindeutigen Identifizierung einer natürlichen Person, Daten zum Sexualleben oder zur sexuellen Orientierung.

Im Falle eines Rücktritts:

☐ Ja, ich bin damit einverstanden, dass - im Falle eines Rücktritts - die bisher erhobenen Daten meiner Person ausgewertet werden.

☐ Nein, ich möchte nicht, dass die bisher erhobenen Daten von meiner Person ausgewertet werden/wird. Es soll sämtliches Material, das mit meiner Person in Zusammenhang steht vernichtet werden

Für Ihre Teilnahme an diesem Forschungsprojekt wären wir Ihnen dankbar.

_____ _____

Ort, Datum Name, Vorname des Teilnehmers

_____

Unterschrift des Teilnehmers

Aufklärende Person:
Der Proband wurde von mir im Rahmen eines Gesprächs über das Ziel und den Ablauf der Studie sowie über die Risiken aufgeklärt. Ein Exemplar der Informationsschrift und der Einwilligungserklärung habe ich dem Probanden ausgehändigt.

_____

Unterschrift des Aufklärenden

Unbeantwortete Fragen: Sollten Sie Fragen haben, wenden Sie sich bitte an den Projektverantwortlichen. Sie haben das Recht, vom Verantwortlichen (s.u.) Auskunft über die von Ihnen gespeicherten personenbezogenen Daten zu verlangen. Ebenfalls können Sie die Berichtigung unzutreffender Daten sowie die Löschung der Daten oder Einschränkung deren Verarbeitung verlangen.
Der Verantwortliche für die studienbedingte Erhebung personenbezogener Daten ist:

Projektverantwortlicher

Apl. Prof. Dr. med. Christoph Nikendei, MME

Christoph.Nikendei@med.uni-heidelberg.de

Oberarzt
Universitätsklinikum Heidelberg
Klinik für Allgemeine Innere Medizin und Psychosomatik
am Universitätsklinikum Heidelberg

Thibautstr. 4
69115 Heidelberg

Bei Anliegen zur Datenverarbeitung und zur Einhaltung der datenschutzrechtlichen Anforderungen können Sie sich an folgenden Datenschutzbeauftragten der Einrichtung wenden:

Datenschutzbeauftragter des Universitätsklinikums Heidelberg
Im Neuenheimer Feld 672
69120 Heidelberg
06221 56 7036
datenschutz@med.uni-heidelberg.de

Im Falle einer rechtswidrigen Datenverarbeitung haben Sie das Recht, sich bei folgender Aufsichtsbehörde zu beschweren:
Der Landesbeauftragte für den Datenschutz und die Informationsfreiheit Baden- Württemberg
Postfach 10 29 32, 70025 Stuttgart
Königstraße 10a, 70173 Stuttgart
Tel.: 0711/61 55 41 – 0
Fax: 0711/61 55 41 – 15
E-Mail: poststelle@lfdi.bwl.de
Internet: http://www.baden-wuerttemberg.datenschutz.de

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Ihr persönlicher Code:

Unter „Pseudonymisierung“ versteht man die Verarbeitung personenbezogener Daten in einer Weise, dass die personenbezogenen Daten ohne Hinzuziehung zusätzlicher Informationen („Schlüssel“) nicht mehr einer spezifischen betroffenen Person zugeordnet werden können. Diese zusätzlichen Informationen werden dabei gesondert aufbewahrt und unterliegen technischen und organisatorischen Maßnahmen, die gewährleisten, dass die personenbezogenen Daten nicht einer identifizierten oder identifizierbaren natürlichen Person zugewiesen werden.

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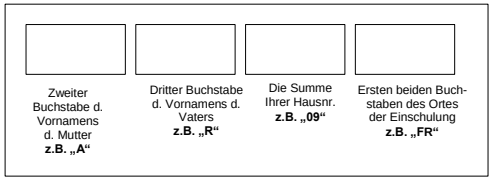
- den **dritten** Buchstaben des Vornamens Ihres Vaters (z.B. „R“ für Herbert)
- die Summe ihrer **Hausnummer** als zweistellige Zahl (z.B. „09“ für Hausnr. 18)
- die **ersten beiden Buchstaben** des Ortes Ihrer Einschulung (z.B. „Fr“ für Frankfurt).



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Zentrum für Psychosoziale Medizin

Klinik für Psychosomatische u. Allgemeine Klinische Medizin

Prof. Dr. med. W. Herzog
Ärztlicher Direktor

Standort Bergheim
Prof. Dr. med. H. Schauenburg
Leiter und geschäftsführender Oberarzt
apl. Prof Dr. med. C. Nikendei, MME
Ltd. Oberarzt, Leiter der Ambulanz

Patienteninformation zur Studie

„Psychische Belastung nach Ruptur der Chordae tendineae“

Sehr geehrte Patientin, sehr geehrter Patient,

Sie sind aufgrund einer Herzklappenerkrankungen in unserer kardiologischen Ambulanz in Behandlung. Im Rahmen dieser Erkrankung haben Sie einen Sehnenfadenabriss oder eine sogenannte *Ruptur der Chordae tendineae* erlebt. Die Sehnenfäden sind dafür da, dass die Herzklappen dicht schließen und das Herz richtig pumpen kann. Wenn die Sehnenfäden reißen, schließt die betroffene Herzklappe nicht mehr richtig und wird undicht (Klappeninsuffizienz), typische Symptome sind u.a. Atemnot und Leistungsschwäche. Bei undichten Klappen muss der Herzmuskel mehr oder stärker pumpen, wird dadurch höher beansprucht und kann schließlich versagen und muss deshalb kardiologisch behandelt werden. Sie wurden aufgrund dieser Undichtigkeit der sogenannten Mitralklappe im linken Teil des Herzens (Mitralklappeninsuffizienz) mit einer kardiologischen Maßnahme (MitraClip®) behandelt. In Kooperation mit der kardiologischen Abteilung wird derzeit von der Abteilung für Psychosomatik der Universitätsklinik Heidelberg eine wissenschaftliche Studie durchgeführt, die die psychischen Auswirkungen des Sehnenfadenabrisses untersucht.

Wir würden Sie gerne für die Teilnahme an vorliegender Studie gewinnen. Bitte lesen Sie sich die folgenden Informationen aufmerksam durch. Eventuelle Fragen beantworten wir Ihnen gerne.

Ziel der Studie

Es ist bisher wenig über die psychischen Belastungsreaktionen nach einem Sehnenfadenabriss bekannt. Jedoch weiß man, dass es im Rahmen von Herzerkrankungen zu Belastungsreaktionen kommen kann, welche bis hin zur sogenannten *posttraumatischen Belastungsstörung* führen können. Auf ein traumatisches Erlebnis, wie etwa eine akute Verschlechterung des Gesundheitszustands, reagiert jeder Mensch auf seine eigene Art und Weise. Trotzdem gibt es Reaktionen, die bei vielen gleich sind. In der Zeit nach einem traumatischen Erlebnis können manchmal ungewollt Bilder, Geräusche, andere Empfindungen und Gedanken an das Erlebnis auftauchen.
Wir möchten in dieser Studie die psychischen Belastungen nach einem Sehnenfadenabrisserfassen. Dabei möchten wir erfahren, welche Gefühle, Gedanken und körperliche Empfindungen Sie im Zusammenhang mit dem Sehnenfadenabriss erlebt haben und wie ihr aktuelles Befinden ist. Psychische Belastungen können auch negative Auswirkungen auf die körperliche Gesundheit haben. Darum soll im Rahmen der Studie auch die Strecke, die Sie maximal in 6 Minuten gehen können, untersucht werden.

Ein besseres Verständnis der psychischen Belastungsfaktoren nach einem Sehnenabriss soll helfen, diesen künftig vorzubeugen, entgegenzuwirken und bessere Unterstützungsmöglichkeiten zu entwickeln.

Beschreibung der Studie

Die Untersuchung der beschriebenen Inhalte soll mittels Interviews und einer Fragebogenerhebung erfolgen. Weiterhin soll die Strecke erfasst werden, die Sie maximal innerhalb von 6 Minuten gehen können. Dies wird insgesamt etwa 50 Minuten dauern. Wir bitten Sie zu berichten, wie Sie den Sehnenfadenabriss erlebt haben und einige Fragebögen zu Ihrem Befinden auszufüllen. Ergänzend werden medizinische Informationen über den Sehnenfadenabriss, sowie eventuelle Vorerkrankungen aus Ihrer Patientenakte erhoben.

Mit einigen Teilnehmerinnen und Teilnehmern wird außerdem ein ausführliches, persönliches Interview durchgeführt, welches etwa 30 Minuten dauern wird. Dabei geht es um Veränderungen, die Sie seit dem Sehnenfadenabriss bemerkt haben und wie Sie damit umgehen. Eine Tonaufnahme des Interviews wird gespeichert, verschriftlicht und ohne Verwendung Ihres Namens ausgewertet (Informationen zum Datenschutz weiter unten). Ihren Wünschen entsprechend kann das Interview entweder telefonisch, bei Ihnen Zuhause oder in der kardiologischen Ambulanz des Uniklinikums Heidelberg durchgeführt werden. Die Teilnahme an dem Interview ist freiwillig und Sie können dieses auch ablehnen.

Nutzen und Risiken der Teilnahme an der Studie

Ihre medizinische Behandlung wird durch die Teilnahme an der Studie nicht beeinflusst. Die Befragung mittels Fragebögen und Interview birgt kein bekanntes Risiko. Im Rahmen der Befragungen kann es zu einer verstärkten persönlichen Auseinandersetzung mit den angesprochenen Inhalten (psychische Belastungen, Beziehungsmuster, Persönlichkeitseigenschaften) kommen. Ihr persönlicher Nutzen durch die Teilnahme besteht in der Möglichkeit, Ihre Erfahrungen im Zusammenhang mit dem Sehnenfadenabriss zu teilen und zu reflektieren. Durch die Teilnahme tragen Sie dazu bei, Maßnahmen zu entwickeln, welche psychische Belastung nach einem Sehnenfadenabriss verhindern.

Freiwilligkeit der Teilnahme

Die Teilnahme an der Studie ist freiwillig. Sie können Ihr Einverständnis jederzeit, ohne Angabe von Gründen und ohne Nachteile für Ihre weitere medizinische Versorgung wieder zurückziehen. Bei Rücktritt von der Studie werden wir, falls Sie dies wünschen, die erhobenen Daten vernichten. Wenn Sie zu einem späteren Zeitpunkt von der Studie zurücktreten möchten, setzen Sie sich bitte mit dem Studienleiter Herrn Apl. Prof. Dr. med. Christoph Nikendei (Kontakt siehe unten) in Verbindung.

Was passiert mit meinen Daten?

Alle Ihre Daten werden mit Ihrem Einverständnis zur wissenschaftlichen Auswertung gesammelt und streng vertraulich behandelt. Sie werden unter keinen Umständen an andere, nicht an der Studie beteiligte Personen weitergegeben. Die erhobenen Daten werden ausschließlich für die in dieser Studie angegebenen Zwecke verwendet.

Sie werden an einem für Unbefugte unzugänglichen Ort aufbewahrt und nach 10 Jahren vernichtet.

Datenschutz nach §4 BDSG:

Im Rahmen der Studie werden die ärztliche Schweigepflicht und die Bestimmungen des Bundesdatenschutzgesetzes eingehalten. Ihre Daten und ggf. die Tonaufnahmen werden in pseudonymisierter Form aufgezeichnet, ausgewertet und ggf. in pseudonymisierter Form weitergegeben. Pseudonymisiert bedeutet, dass ein Nummern- und/oder Buchstabencode verwendet wird, ggf. in Kombination mit dem Geburtsjahr (nicht jedoch mit dem vollständigen Geburtsdatum). Eine nachträgliche Zuordnung der Daten zu einer bestimmten Person ist nur mit Hilfe einer Art "Schlüssel" möglich. Zugang zu diesem „Schlüssel" hat ausschließlich der Studienleiter. Dritte erhalten keinen Einblick in Ihre Originalunterlagen. Bei der Veröffentlichung von Ergebnissen der Studie wird Ihr Name nicht genannt.

Wir würden uns freuen, wenn Sie an der Studie teilnehmen!

Leider können wir Ihnen für den Zeitaufwand beim Ausfüllen der Fragebögen sowie das Interview keine Aufwandsentschädigung zukommen lassen.

Für Rückfragen stehen wir Ihnen gerne zur Verfügung:

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BERUFLICHER WERDEGANG

Seit 04/15	*Stationspsychologin* der psychosomatisch-psychotherapeutischen Abendklinik der Klinik für Allgemeine Klinische und Psychosomatische Medizin am Universitätsklinikum Heidelberg.
Seit 01/15	*Wissenschaftliche Mitarbeiterin* in der Klinik für Allgemeine Klinische und Psychosomatische Medizin am Universitätsklinikum Heidelberg.
01/15 – 12/15	*Projektkoordinatorin* des Kompetenzzentrums „Prävention psychischer und psychosomatischer Störungen in der Arbeits- und Ausbildungswelt“ gefördert aus Mitteln des Ministeriums für Wissenschaft, Forschung und Kunst Baden-Württemberg, unter der Federführung des Zentrum für Psychosoziale Medizin Heidelberg. Prof. Dr. med. S. Herpertz und Prof. Dr. med. W. Herzog.
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AKADEMISCHER WERDEGANG

Seit 01/14	Weiterbildung zur Psychologischen Psychotherapeutin mit dem Schwerpunkt psychodynamischer (tiefenpsychologisch fundierter) Psychotherapie am Heidelberger Institut für Psychotherapie (HIP).
10/06 – 09/13	Studium der Psychologie an der Johannes Gutenberg-Universität, Mainz, Deutschland. Abschlussnote: 1,3.
23.06.2005	Abitur. Abschlussnote: 1,8. Goethe Gymnasium, Frankfurt am Main

SPRACHEN Bilingual deutsch-englisch, gute Französischkenntnisse

Acknowledgments

At this point, I would like to thank everybody who supported me during this thesis. It takes a village to raise a child. My special thanks go to the following:

I am deeply grateful to apl. Prof. Dr. med. Chirstoph Nikendei, MME for his generous and continuous support. He has carefully guided me throughout these years and his friendly encouragement has made it possible for me to survive the blue times of low progress: without him, none of this would have been possible. I would like to thank PD Dr. Seven Pleger and Dr. Nicolas Geis for giving me the opportunity of implementing my study in the Department of Cardiology, Heidelberg Medical Hospital and their continuing support through this work.

I am very thankful to Msc. psych. Anja Greinacher and Dr. Anne Klippel for their advise and intellectual support that helped me overcome the most difficult moments throughout this work, and also for the correction of the thesis.

I am deeply indebted to and highly acknowledge Dr. Ede Nagy for his statistical expertise and for the correction of part of this thesis.

To thank my dear friends Miriam for her unwavering support and all the precious time spent together.

I am very grateful for my wonderful brother here and always. Thank you very much, Victor, for your infinite support, round-the-clock services, emergency help, intellectual contributions and all the other things I've forgotten to mention.

My heartfelt gratitude goes to my love, Cyril, who keeps me sane and makes me happy, and my family and friends for their warm encouragement and support during all the years of my scholarly endeavours.

Finally, I am most indebted to all the participants that were willing give me their time and share their experiences as well as return the questionnaires with their responses.

Erklärung

1. Bei der eingereichten Dissertation zu dem Thema
   "Broken Heart Strings - Psychological Stress in Cardiac Patients after Chordae Tendineae Rupture"
   handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

3. Die Arbeit oder Teile davon habe ich bislang nicht an einer Hochschule des In- oder Auslands als Bestandteil einer Prüfungs- oder Qualifikationsleistung vorgelegt.

4. Die Richtigkeit der vorstehenden Erklärungen bestätige ich.

5. Die Bedeutung der eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unrichtigen oder unvollständigen eidesstattlichen Versicherung sind mir bekannt.

   Ich versichere an Eides statt, dass ich nach bestem Wissen die reine Wahrheit erklärt und nichts verschwiegen habe.

Frankfurt am Main, 16th December 2019

Dipl. Psych. Anna Cranz