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Taking mind matters to heart

E-health methods to assess and treat psychological distress associated with myocardial infarction and Takotsubo syndrome

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Abstract

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This thesis comprises five studies investigating psychological distress in patients with myocardial infarction (MI) and Takotsubo syndrome (TS), with a focus on using e-health methods for data collection and delivery of psychological interventions.

The aim of study 1 was to explore the long-term (12 month) effect of an internet-delivered intervention for MI patients experiencing self-reported symptoms of anxiety or depression compared to a control group without access to the treatment intervention. Using data from several Swedish national registers we also investigated whether the intervention had any effect on risk for adverse cardiovascular (CV) events, including recurrent MI and CV-related mortality. Effect of treatment was not significant between groups on lowering symptoms of anxiety or depression nor for risk of CV events or CV-related mortality. Low treatment adherence is discussed as a probable reason for these findings.

Study 2 aimed to build from the lessons learned in study 1, as well as the existing literature and continuous input and collaboration with patient research partners (PRPs) to develop an internet intervention designed for patients experiencing high levels of anxiety or stress following MI with non-obstructed coronary arteries (MINOCA) or TS. We present the processes involved during the development and creation of this novel internet intervention. Following on from this, in Study 3 we tested the feasibility of this intervention using pre-specified progression criteria that was aimed to assess whether the intervention and study protocol were feasible in a randomised controlled trial (RCT). We screened patients for eligibility and offered participation in the study to those who met the pre-defined inclusion criteria. We collected both psychometric and qualitative data and assessed progression criteria that covered: recruitment, time and resources, proportion of participants completing the intervention and, participant experiences of the intervention.

Study 4 used data from the Swedish national registers to estimate the association of health-related quality of life (HRQoL) with high vs low dose of β-blocker, prescribed after MI. The aim was to investigate, in advance of an ongoing register-based RCT, whether there is any association of β-blocker dose on patient reported HRQoL. Since there are many reasons for a patient to receive a high or low dose respectively, controlling for possible confounding was crucial. We used the European Quality of Life Five Dimensions questionnaire (EQ-5D) to assess HRQoL using data from over 35000 unique, first-time MI patients in Sweden.

Study 5 presents the trial design, rationale and baseline data from the first 100 patients recruited into a registry-based RCT sub-study focussed on investigating several psychological-related outcomes in patients randomised to receive β-blocker treatment or no treatment. The feasibility, strengths and challenges of using digitalised in-hospital data collection techniques are also evaluated.

Keywords: Myocardial infarction, psychological distress, Takotsubo syndrome, Myocardial infarction with non-obstructed coronary arteries, iCBT

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Tomorrow turns a loss to a lesson,
a curse into a gift and a blessing

List of Papers

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

I. Humphries SM, Wallert J, Norlund F, Wallin E, Burell G, von Essen L, Held C, Olsson EMG. (2021) Internet-based Cognitive Behavioral Therapy for Patients Reporting Symptoms of Anxiety and Depression after Myocardial Infarction: U-CARE Heart Randomized Controlled Trial Twelve-Month Follow-up. *Journal of Medical Internet Research* 23(5):1–14.

II. Humphries, S.M., Rondung, E., Norlund, F., Sundin, Ö., Tornvall, P., Held, C., Spaak, J., Lyngå, P., Olsson, E.M.G., (2020) Designing a Web-Based Psychological Intervention for Patients With Myocardial Infarction With Nonobstructive Coronary Arteries: User-Centered Design Approach. *Journal of Medical Internet Research* 17;22(9):e19066.

III. Rondung, E., Humphries, S.M., Olsson, E.M.G., Sundelin, R., Norlund, F., Held, C., Spaak, J., Tornvall, P., Lyngå, P. (2022) Reducing Stress and Anxiety in Patients with Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) or Takotsubo Syndrome: A Non-Randomized Feasibility Study. Submitted.

IV. Humphries*, S.M., Wallert*, J., Mars, K., Held, C., Hofmann, R., and Olsson, E.M.G. (2022) Association Between β-Blocker Dose and Quality of Life after Myocardial Infarction. A Real-World SWEDEHEART-Linked Register Study. Submitted.

V. Humphries, S.M., Mars, K., Hofmann, R., Held, C., and Olsson, E.M.G. (2022) Randomized Evaluation of Decreased Usage of β-Blockers after Myocardial Infarction: Quality of Life (R-Qol): Design and Feasibility of a Multicenter, Prospective, Randomized, Open, Blinded Endpoint Study. Manuscript.

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Contents

Abbreviations

ACE inhibitors	Angiotensin-converting enzyme (ACE) inhibitors
ACS	Acute coronary syndrome
ADePT	A process for Decision-making after Pilot and feasibility Trials
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ASEX	Arizona Sexual Experiences Scale
BADS-SF	Behavioural Activation for Depression Scale-Short Form
BMI	Body mass index
BMQ	Beliefs about Medicines Questionnaire
CAD	Coronary Artery Disease
CAQ	Cardiac Anxiety Questionnaire
CBT	Cognitive Behavioural Therapy
CCU	Coronary care unit
CHD	Coronary Heart Disease
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CVD	Cardiovascular Disease
DALY	Daily Adjusted Life Year

ECG	Electrocardiogram
EF	Ejection fraction
EQ5D-3L	European QoL 5 Dimensions Questionnaire 3-Levels
EQ5D-I	EQ5D Index score
EQ5D-VAS	EQ5D VAS Scale
ESC	European Society of Cardiology
eSMINC	E-health Treatment of Stress and Anxiety in Stockholm Myocardial Infarction with Non-obstructive Coronaries study
FGD	Focus group discussion
HADS	Hospital Anxiety and Depression Scale
HDL	High-density lipoprotein
HRQoL	Health-related quality of life
iCBT	Internet-based cognitive behavioural therapy
ICD	International Classification of Disease System
IES-6	Impact of Event Scale 6-item version
ITT	Intention-to-treat
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular event
MADRS-S	Montgomery Åsbery Depression Rating Scale Self-rated
MI	Myocardial Infarction
MINOCA	Myocardial Infarction and Non-Obstructive Coronary Arteries

NICE	National Institute for Health and Care Excellence
NPR	National Patient Register
PDR	Prescribed Drug Registry
PPI	Patient and Public Involvement
PRP	Patient research partner
PSS-14	Perceived Stress Scale 14-item survey
PTSD	Post-traumatic Stress Disorder
QoL	Quality of life
RAND-36	RAND Short-Form 36-item survey
RCT	Randomised controlled trial
REDUCE	Randomized Evaluation of Decreased Use of Beta-blockers after Acute Myocardial Infarction
RIKS-HIA	Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admissions
RQoL	REDUCE: QoL study
RRCT	Registry-based randomised controlled trial
SBP	Systolic blood pressure
SEPHIA	Secondary Prevention after Heart Intensive Care Admission
SPIRIT	Standard Protocol Items for Clinical Trials and related documents
SWEDE-HEART	Swedish Web-system for Enhancement and Development of Evidence-based Care in Heart disease Evaluated According to Recommended Therapies
TAU	Treatment as usual
TS	Takotsubo Syndrome

U-CARE Portal	Uppsala University Psychosocial Care Programme (U-CARE) Portal
WHO-5	World Health Organisation-Five Well-Being Index

Introduction

Cardiovascular disease

Myocardial infarction

Despite improvements of care in the last few decades, cardiovascular disease (CVD) is the leading cause of death globally [1]. Acute coronary events such as myocardial infarction (MI) can occur as a result of coronary heart disease (CHD), where blood flow to the heart muscle, the myocardium, is restricted by atherosclerotic stenosis in the coronary arteries leading to myocardial damage. An acute MI can be triggered by various factors (such as physical exertion, anger or cocaine use) [2], but is often caused by a ruptured plaque in a patient with underlying presence of CHD.

The global burden of CHD, as measured in disability-adjusted life years (DALYs), includes death or disability due to myocardial infarction (MI) and has increased markedly over the last few decades which is largely attributable to the ageing of the population [1]. Improvements in diagnostics, medical treatment and secondary prevention have led to a remarkable decrease in the mortality rate due to MI in Sweden [3], with the greatest decrease seen between the 1990s and 2010. Despite this, a plateau has been observed in recent years and CVD (including MI) continues to be the leading cause of death in Sweden for both men and women [4].

Apart from genetic predisposition to early onset CVD [5] the factors with the highest risk for MI are mostly lifestyle related and potentially modifiable, such as current smoking, ApoB/ApoA1 ratio (or alternatively the ratio of LDL to HDL cholesterol, or so-called “good” vs “bad” cholesterol), diabetes and psychosocial factors [6]. They explain up to 90% of the total risk. These risk factors are in turn associated with psychosocial factors (such as education level) as well as with medication adherence and behavioural change [7] and thus play a complex role in the maintenance of behavioural risk factors.

MINOCA and Takotsubo syndrome

Myocardial infarction and non-obstructive coronary arteries (MINOCA) is briefly defined by the European Society of Cardiology (ESC) as a diagnosis given to MI patients with no angiographic obstructive coronary artery disease (CAD) (≥50% obstruction) [8]. Prevalence is estimated to be between 6-8%

of patients diagnosed with MI, although the exact data to confirm these figures is somewhat obscure [9,10]. In many cases, the definitive cause of MINOCA is not entirely known, yet it is more common among women than men who are also younger on average than MI patients with obstructive CAD [11,12].

Takotsubo syndrome (TS), like MINOCA, mimics to some extent the presentation of MI with acute chest pain and elevated Troponins, indicating a myocardial injury. However, echocardiographic examination shows a characteristic pattern with a temporary akinesia in the apical parts of the left ventricle and typical narrowing of the base of the left ventricle, which impairs the left ventricular function and ability to pump blood. Obstructive CAD is present in fewer than 15% of TS cases and the onset of TS is commonly in tangent with an emotionally or physically stressful event [13,14]. TS is estimated in approximately 1-2% of suspected acute coronary syndrome or MI patients. The pathophysiology of TS is still not entirely clear despite over 25 years since its recognition. TS has been considered as a cardiomyopathy, a term for diseases of the heart muscle which affect the heart's ability to pump blood around the body. TS was previously included under the umbrella-term MINOCA and as such was classified as so, however guidelines from the ESC recently excluded TS from the current definition of MINOCA [15].

Secondary Prevention following MI

Cardiac Rehabilitation

In Sweden the incidence of MI including fatal and non-fatal MIs, was reported to be around 22,000 in the year 2020. The current usual care after MI includes a cardiac rehabilitation programme that focuses largely on secondary prevention i.e. reducing the risk for CVD or re-infarction. Most risk factors for MI are lifestyle-related [6] and explain more than 90% of the risk, therefore are potentially modifiable. Thus, it is extremely important that patients take an active role to try to improve these risk factors. Cardiac rehabilitation is largely focussed on targeting these modifiable risk behaviours and includes a programme that is led by a physiotherapist to encourage physical training as well as a group educational programme called Heart School. This is a semi-structured programme aiming to educate patients and their close relations about coronary heart disease, its risk factors and what can be done to reduce the risk of recurrent events. These targets are not only to make changes such as taking up more exercise, stopping smoking and lowering blood cholesterol, but also for aspects related to taking medication, minimising stress and learning about psychosocial risk factors.

The uptake of patients taking part in cardiac rehabilitation programmes in Sweden is generally high. Despite the COVID-19 pandemic, a move to a digital-based heart school and telephone follow-up as well as increased uptake of

cholesterol absorption inhibitor medication meant that improvements to systolic blood pressure (SBP) and LDL-cholesterol goals has further increased in comparison to the previous year [16]. However, many targets have remained unchanged over the last few years indicating areas for improvement as well as the importance of increasing participation in cardiac rehabilitation in general.

Beta-blockers

As well as lifestyle changes, secondary prevention also includes pharmacological therapies largely aimed at preventing blood clots, controlling blood pressure and lipid levels. β-blockers have since long been prescribed as a standard drug treatment following MI for several decades to prevent recurrent MI. The first major trials to investigate the efficacy of β-blockers were performed in the 80s and revealed that β-blockers were important for increased survival rates after MI [17,18]. Such trials have yet to be sufficiently replicated in contemporary MI populations (yet trials are underway in Europe, see Clinical Trials no: NCT03278509 and NCT03596385) since the introduction of newer, modern treatments such as statins, reperfusion therapy and Angiotensin-converting enzyme (ACE) inhibitors [19,20]. For patients with left ventricular ejection fraction (LVEF) below 40%, treatment with β-blockers is recommended in guidelines and widely accepted among cardiologists [21]. Treating patients with β-blockers with LVEF ≥50%, otherwise regarded as normal LVEF, is however, more debated since the evidence is weak. Since the introduction of modern drug therapies the efficacy of prescribing β-blockers in this group is therefore under question [22]. Further, many patients report side effects while taking β-blockers such as sleep disturbances and sexual dysfunction [23,24]. Thus, leaving out β-blockers as routine treatment to this population may have positive effects on their quality of life (QoL).

Mental health in the cardiac population

Mental health following a cardiac event

For many people, experiencing a coronary event may result in increased emotional distress and lowered health-related quality of life (HRQoL), including anxiety and depression symptoms, particularly in the long-term [25]. A large registry-based study of over 27,000 first-time MI patients in Sweden showed that around 38% of patients report symptoms of emotional distress at 2-months post-hospital discharge and just over 30% report elevated symptom levels also at 12-months post-MI [26]. This finding appears to be even more pronounced in those with persistent levels of emotional distress at 12-months after MI, whilst patients who report remittent distress, appear to show more

favourable outcomes at 12 months post-MI [27]. Offering treatment to improve the mental health of patients both at-risk for CVD, and following MI, is important for cardiovascular health, since the relationship between psychological distress and MI appears to be bi-directional. Depression has reported to be associated with a 31% increased risk of a recurrent MI and 36% increased risk of coronary death [28] and likewise, treating patients with elevated levels of depression following MI reduces the likelihood of re-infarction [29]. Likewise, type D personality (which is more commonly occurring in MI and TS patients [30]) and its accompanying tendencies, such as experiencing negative emotions and social inhibition, have been linked with worse cardiac prognosis in CAD patients [31]. Reducing (or treating) emotional distress that is present following MI is therefore important for long-term mental health outcomes.

This relationship between psychological health and cardiac health is not limited to patients with MI. Pre-existing mental health disorders have been associated with increased risk for both MINOCA and TS [32–34]. Furthermore, since MINOCA and TS are both relatively uncommon diagnoses, many patients diagnosed are not familiar with the term nor comprehend its meaning [35]. This is often coupled with vague explanations from healthcare staff, which can further worsen anxiety [30]. The risk of experiencing emotional distress for patients with MINOCA is reportedly higher than those with MI (with CAD) or controls [36]. In addition, around a third of patients have had a previous diagnosis of psychiatric illness beforehand of which psychological disorders including, anxiety and mood disorders, were the most common reported type of comorbidity [32,37].

Psychosocial care for patients with MI and Takotsubo syndrome

Hospitals in Sweden seldom involve psychologists as part of the broader cardiac healthcare team involved with cardiac rehabilitation and secondary prevention. Yet, international guidelines by the ESC recommend screening patients with established CHD for psychosocial risk factors and offering referral to adequate psychological care in the case of clinically diagnosed mental illness [38]. The national guidelines in Sweden for heart-related medical care recommend referral of cardiac patients with signs of depression, anxiety or high stress to a psychologist, primary care and/or stress management [39]. Despite this, patients with comorbid mental health disorders still have higher mortality after MI and have lower compliance to secondary preventative medical treatment than those without [40]. In addition, the ESC reports that there are large gaps in the implementation of cardiac rehabilitation and that only up to a half of eligible patients are referred to secondary prevention or end up taking up the programme [41]. An ESC survey that included respondents from 24 European countries supported the claim that this uptake of cardiac rehabilitation as part of secondary prevention is sub-optimal [42]. MINOCA patients

are even less likely to reach secondary prevention targets and less likely to be followed-up than patients with MI (with CAD) [43].

With such a great importance placed on the psychological consequences of experiencing a cardiac event such as MI, the demand for resources to deliver the adequate care is understandably high. Screening for depression in patients with CVD is feasible, reasonably time consuming and the response rate is satisfactory [44]. However debate has arisen in regard to the effectiveness of such screening since few studies have demonstrated significant effects on clinical outcomes [45]. Regardless, guidelines should be followed closely in regards to screening for mental health problems in patients following MI and the lack of adequate psychological care needs to be addressed.

Interventions to Improve Mental Health in MI Patients

Cognitive behavioural therapy (CBT) has long since been used in the treatment of mood and anxiety disorders. CBT is an appropriate treatment for subthreshold symptoms and mild to moderate common mental health disorders as recommended in the guidelines from the National Institute for Health and Care Excellence (NICE) [46].

Several trials have already shown a positive effect of in-person CBT in reducing the recurrence of CVD events [29] as well as in reducing psychological symptoms such as somatic anxiety and improvements in depressive symptoms [47,48]. A recent meta-analysis that reviewed 35 studies reported that psychological interventions improved depressive symptoms, stress, and anxiety compared to controls as well as showing a reduction in cardiovascular mortality [49]. Similar reviews have also supported these findings [50,51]. Researchers have in recent years investigated the effectiveness of such therapy when provided via the internet on outcomes such as stress [52,53]. Reviews have demonstrated it is both acceptable and effective for patients with anxiety and depression symptoms [54,55].

Digital Interventions

Using the internet as a delivery platform

Internet-delivered therapy is one way that we can try to ensure people have access to therapy, particularly in cases where traditional face-to-face therapy is not feasible [55]. Older adults often report barriers to face-to-face therapy, such as cost and transportation difficulties [56,57] making iCBT a possible and preferable solution, as it is perceived as more easily accessible, convenient and affordable, compared to face-to-face CBT [58,59]. Since the introduction of online forms of therapy, several trials have evaluated the effectiveness of

internet delivered therapy against traditional forms, with promising, albeit varied, results [54,60]. Internet-delivered therapy has also been shown to be effective when compared to treatment as usual (TAU) in participants recruited both clinically and in the community as well as effective at preventing major depression even at a 12-month follow-up [61,62].

There are however, several challenges and limitations to internet-delivered therapy. Largely, these involve low adherence to treatment and as is often the case with internet interventions, many patients report that there is too high a demand on concentration/reading and writing skills, and that it does not fulfil a perceived need for face-to-face contact [63,64].

Developing digital interventions

Creating digital interventions is a complicated and careful process that involves many challenges and factors to consider, especially when it comes to evaluation of new interventions. Prospective controlled trials are extremely important in intervention research, particularly as evidence for spontaneous remission of symptoms of anxiety and depression, without treatment, is quite strong [65,66]. Trials should be carefully planned and development literature should thus be utilised, where possible, beforehand.

Suggested research questions that should be addressed when developing digital interventions are outlined in Table 1.

Table 1 Suggested research questions needed to appraise digital health interventions (adapted from the work of Murray and colleagues [67])

Acceptability and **usability,** (will the target audience (e.g. patients) incorporate and sustain the intervention into their lives/clinical practice?)
Demand, (will relevant stakeholders use it?)
Implementation, (will it have high fidelity within real-world use?)
Practicability, (can it be delivered with minimal burden?)
Adaptation, (can it be adapted to novel contexts without compromising fidelity and integrity?)
Integration, (can it be integrated successfully into existing healthcare systems?)

However, important to consider in the development of a new intervention, regardless of its delivery method, is the involvement of the intended target-group. This can be achieved through the use of patient participatory methods, namely, patient and public involvement (PPI). PPI helps to identify the needs of the user in question so that the intervention is relevant to them and can even

help researchers to develop a greater understanding of their research area [68,69].

Involving patients in digital intervention research

It is argued that the knowledge gained from working with the public is more useful to society and leads to better research [70]. Several research journals even invite patients and members of the public to be involved in the peer review process, demonstrating a desire to ensure that research is both relevant and appropriate to its end-users. Yet, in a recent survey, over 90% of involved patient and public reviewers reported that they thought more journals should be co-operating with public, thus suggesting there is much room for improvement [71]. Even when studies have consulted with patients, several elements of the intervention have not always been well-adjusted enough to meet the needs of the user and have been reported as irrelevant or too demanding, despite efforts made to avoid this [72]. Using a patient-centred approach by involving patients in the design and development process is arguably the most effective way to build novel interventions that are aimed at a unique patient group, such as those with MINOCA or TS [73]. The idea behind PPI in research is to allow members outside of the research community to contribute in a way that increases the relevancy and insightfulness of research to those who are part of the target group [68,69]. In study II we took these principles of working with members outside of the research team to ensure PPI was a key part of the study process.

Feasibility trials and the importance of feasibility testing

Many trials face problems during conduction that are often due to the study design and can lead to challenges with, for example: recruitment, study pace, adherence and outcomes. This can lead to heavily delayed studies and in some cases, discontinuation. The proportion of trials that have reported results through publication in scientific journals, or by other means after an abstract presentation, was reported to be 59.8% for randomised controlled trials (RCTs) and as low as 37.3% for RCTs and controlled trials overall, according to a recent Cochrane review [74]. Similar rates have been reported elsewhere when looking at proceeding publication of full trials that have received approval by ethics committees or have published a trial protocol in a trial register [75–77].

Feasibility trials and internal pilot designs aim to carefully evaluate the likelihood of success of the main trial and assess factors such as recruitment, trial adherence and intervention outcomes. A large aim of such trials is to identify potential issues before the start of the main trial so that amendments can be made in order to prevent these potential problems during the RCT [78]. Areas to consider when deciding pre-defined progression criteria are not

strictly guided but some suggestions and considerations when developing progression criteria for RCTs have been published [79].

Swedish national registers

Sweden is one of the most vast and data-rich European countries when it comes to its national registers, boasting wide coverage and quality data reportage that is regulated by Swedish law. The procedures for data collection and maintenance can differ between registers, but since they are well-regulated and linked by each individual's personal identification number, analysing data from multiple registers is quite simple. Furthermore, since the registers operate an opt-out procedure (i.e. waived consent), patients are entered into the registers by default, unless they do not wish to be (i.e. opt-out), meaning that coverage is generally exceptionally high.

The following Swedish national registers were utilised in the included studies from the Swedish National Board of Health and Welfare (Socialstyrelsen) (i) the National Patient Register (NPR), (ii) the Cause of Death Register, and (iii) the Prescribed Drug Registry (PDR). These are all extensive high-quality registers linked to Swedish residents through a personal identification number that is unique to each individual [80]. The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) is a complete quality, national register on CVD in Sweden [16]. SWEDEHEART collects relevant information regarding risk profile, medical treatment, among other variables, and can make comparisons between hospitals as well as regions. One component registry of SWEDEHEART, the Register for Information and Knowledge on Heart Intensive Care Admission (RIKS-HIA) is the Swedish register for intensive heart care and collects more than 100 variables from those included with acute coronary syndrome, currently with a median coverage in Swedish hospitals of approximately 96% of all MIs [81]. The second largest of SWEDEHEART's registers, the registry for secondary Prevention after Heart Intensive Care Admission (SEPHIA), collects data at two time points (6-10 weeks following the acute MI and again at 12-14 months post MI) on lifestyle, psychosocial and other secondary preventative factors. SEPHIA coincides with hospital visits appointed with the cardiologist. These two registers provided many of the patient background and health-related variables for studies I, IV and V.

Aims

This project covers several areas within the field of cardiovascular-related psychological distress and aims to improve our understanding in this area so we can contribute towards better mental health for patients with MI or Takotsubo syndrome.
The study specific aims were:

I. To investigate, in an RCT, the long-term effect of an iCBT treatment on symptoms of depression and anxiety and whether the treatment had any effect on clinical outcomes including incidence of CVD and CVD-related mortality.
II. To use gained experience from study I, existing literature and insights from collaborating with patient research partners (PRPs) to develop a novel internet intervention for patients experiencing high levels of anxiety and stress following a recent TS event or MINOCA.
III. To evaluate the intervention developed in study II in regards to the overall feasibility and projected success of the planned RCT. Several progression criteria were aimed to be taken into account for evaluation: 1. Recruitment, 2. Time and resources, 3. Proportion of participants completing the intervention and 4. Participant experiences of the intervention.
IV. To explore the association of β-blocker dose with HRQoL in patients with first-time MI, using the Swedish national registers.
V. To further investigate the relationship of β-blockers on HRQoL in a randomised controlled trial comparing treatment vs no treatment. We aimed to present the trial design and baseline data from the first 100 recruited patients as well as the strengths and challenges of using digitalised in-hospital data collection techniques.

Ethical Considerations

All studies adhered to the Declaration of Helsinki and were conducted in accordance with the ethical principles for medical research involving human subjects. Further to this, the studies' protocols were registered on ClinicalTrials.gov prior to commencement and all studies received ethical approval from the regional Ethical Review Board in Uppsala (studies I and IV) or Stockholm (Studies II, III and V). Written informed consent was provided by all participants in Studies I-III and V, provided by pen and paper or signed digitally and authenticated by BankID authentication. Study IV used data from the Swedish national registers where the opt-out (waived consent) method applies. Approval for the access of data is decided by the responsible ethical review board and all patients are informed of (i) the opt-out procedure, (ii) the approved uses of the data and (iii) whom can be approved to order access to the data.

Data were stored in secure servers and coded to protect the identity of the participants. Sensitive information that was in physical paper form were stored in a secure protected vault, with access limited only to some of the research team. Data protection and storage policies were followed tightly in accordance with the General Data Protection Regulation policy (GDPR).

Methods

Overview of papers

Table 2 Overview of the five studies with regards to the methodological elements involved, including study design, participants, data collection and analysis

Paper	Design	Participants	Data	Analysis
Paper I	RCT	239 participants	Standardised questionnaires, register data	Multiple linear regression, Cox regression
Paper II	Participatory	7 PRPs	FGDs, semi-structured interviews, research group meetings	Descriptive
Paper III	Feasibility (non-randomised)	9 participants with MINOCA or TS	Standardised questionnaires, semi-structured interviews, feasibility progression criteria	Descriptive, effect size analysis
Paper IV	Observational	35612 MI patients	Register data	Linear and logistic regression
Paper V	Methodological, descriptive	First 100 patients in RQoL	Standardised questionnaires, register data	Descriptive statistics

RCT, randomised controlled trial; PRPs, Patient Research Partners; MINOCA, myocardial infarction with non-obstructive coronary arteries; TS, Takotsubo syndrome; MI, myocardial infarction; RQoL; REDUCe: Quality of Life; FGDs, focus group discussions

Shared methods Study I-V

Questionnaires measuring anxiety and depression

The Hospital Anxiety and Depression Scale (HADS)[82] is a 14-item self-report scale for measuring symptoms of depression and anxiety. Each item is

given a rank 0-4 and summed together to compute the HADS total score (HADS-T). The HADS anxiety (HADS-A) and depression (HADS-D) scores are computed by calculating the score of the items pertaining to each subscale, that is 7 of the 14 items that measure anxiety and the remaining 7 that measure depression. These subscales were included as measures in Study I, Study III and Study V. A score of >7 is indicative of borderline abnormal levels of depression and/or anxiety. The HADS has been used and recommended for the screening of depression among cardiac patients [83].

The Cardiac Anxiety Questionnaire (CAQ)[84] measures heart-focused anxiety and contains 18 items, broken down into three subscales (8 items measuring heart-related fear, 5 items measuring avoidance and 5 items measuring attention). Each item is rated 0-4 on a 5-point Likert scale (never, rarely, sometimes, often, always). The CAQ features in Study I, Study III and Study V.

Other self-report questionnaires measuring depression included only in Study I were: the Montgomery-Åsberg Depression Rating Scale Self-rated (MADRS-S)[85] and the Behavioural Activation for Depression Scale-Short Form (BADS-SF) [86].

Questionnaires measuring HRQoL

The RAND Short-Form 36-item survey (RAND-36) is a 36-item questionnaire that measures HRQoL across eight health concepts (physical functioning, pain, limitations due to physical health, limitations due to personal or emotional problems, emotional wellbeing, social functioning, energy/fatigue and general health perceptions [87].

The European Quality of Life Five Dimensions Questionnaire (EQ5D) 3-level version (EQ5D-3L) [88] is a standardised questionnaire measuring health-related quality of life (HRQoL). The EQ5D-3L is administered during both SEPHIA follow-ups. It contains five questionnaire items with 3 response levels (1 = “no problems”, 2 = “some problems”, 3 = “extreme problems”) across five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). The visual analogue scale (VAS) is the second part of the EQ5D questionnaire whereby respondents mark their current self-perceived health state on a scale of 0-100 (0 = worst imaginable health state and 100 = best imaginable health state).

Questionnaires measuring stress-related disorders

The Impact of Event Scale (IES-6) [89] is a short 6-item questionnaire designed to capture severity of symptoms, covering three symptom clusters of post-traumatic stress disorder (PTSD): intrusion, avoidance and hyperarousal.

The Perceived Stress Scale (PSS-14) [90] is designed to measure the degree to which a person perceives their life situations as stressful. Fourteen questions are rated on a 0-4 5-point Likert scale and responses relate to the past month.

Other health-based questionnaires

The Beliefs about Medicines Questionnaire (BMQ) [91] is a questionnaire with two scales divided into the BMQ-specific (assessing attitudes towards medication prescribed for personal use) and BMQ-general (assessing beliefs about medicine in general). Both scales contain responses on a 5-level response scale (strongly agree, agree, uncertain, disagree or strongly disagree).

The Arizona Sexual Experiences Scale (ASEX) [92] assesses sexual functioning with 5 questions pertaining to sexual functioning and satisfaction in both male- or female-identifying respondents. Six-level responses (1-6) mean that the total score can range between 5 and 30, with a score >19 indicating "sexual dysfunction". In clinical settings the ASEX has been shown to be a reliable instrument for identifying sexual dysfunction [93].

The World Health Organisation- Five Wellbeing Index (WHO-5) [94] is a short questionnaire measuring self-reported current wellbeing. Five statements are rated on a six-point scale (0 = At no time, 5 = All of the time) in relation to the past two weeks, to give a score ranging from 0 to 25 which is then multiplied by 4 to produce a total score, where 0 represents the worst imaginable wellbeing, and 100 the best.

The U-CARE Portal

The Uppsala University Psychosocial Care Program (U-CARE) Portal is an internet-based platform designed to operate studies (observational, RCTs etc.), enable collection of data and deliver interventions such as internet-based psychological therapies. The portal is optimised for computer, mobile phone and tablet devices and is therefore accessible for most uses. As well as study functions and data collection, it is possible to collect signed consent via the portal when entering a new study. Other features also include content libraries (specific to each study), chat and messaging functions, automatic randomisation and automatic short message service (SMS)/e-mail/internal message reminders.

The portal's high security design means that data are secure and logging in is done through either double SMS authentication or with BankID.

Study I

Aims and research question

The aim of Study 1 was to explore the long-term follow up of an internet-based CBT intervention (the U-CARE Heart Trial) for patients with MI and symptoms of anxiety or depression. The post-intervention results from the initial trial found no significant effect of iCBT on anxiety or depression symptoms versus treatment as usual [72]. Our aim was to investigate whether results were similar at the 12 month follow-up. To investigate further and ensure we could benefit from the longitudinal aspect while adding to the previous study's findings, we collected additional data from the NPR, National Board of Health and Welfare and several of the SWEDEHEART registers to analyse the potential effect of iCBT treatment on cardiovascular outcomes and mortality.

Study participants and procedure

Study I was based on the U-CARE Heart trial [72] which investigated, but did not find, a post-treatment effect of a 14-week iCBT programme for MI patients with low-to-moderate levels of anxiety and/or depression. Since this study used data collected 12-months post-MI, the study design, participants and procedure were the same. The study included patients <75 years of age with a recent MI (no more than 3 months), and a score >7 on either or both of the HADS subscales. Participants scheduled for coronary artery bypass surgery were not eligible, nor were those unable or unwilling to use the internet, computer, or a mobile phone, as well as those unable to read or understand Swedish. Life expectancy of less than a year and anticipated low compliance were also exclusion criteria. This resulted in a total of 239 patients that were randomised to receive iCBT (n=117) or treatment as usual ((TAU), n=122).

Treatment intervention

The intervention was a 14-week treatment programme that was delivered online and guided by psychologists. The iCBT treatment was adapted from traditional face-to-face CBT and was created with focus on cardiac patients. This meant that many of the treatment modules used examples that were relevant to people with a recent MI and included supplementary library materials as well as interviews with MI patients and video clips that focused on common psychological reactions after MI. Assignments were also part of the treatment and participants were given feedback from their designated psychologist on these, as well as being able to communicate with their psychologist through the U-CARE portal, if needed. The introductory module was the only compulsory one, whereas participants could then chose to work with two or three of the remaining 10 modules: (i) Worry management; (ii) Fear and avoidance

after MI; (iii) Behavioural activation; (iv) Problem solving; (v) Communication training; (vi) Relaxation; (vii) Cognitive restructuring; (viii) Coping with insomnia; (ix) Values in life; (x) Relapse prevention.

In the case of inactivity on the Portal, participants were reminded by automatic SMS and email notifications, if still inactive they were contacted via telephone or post (preference-dependent) and encouraged to continue with the treatment.

Data Collection

This study collected and analysed psychological self-reported data collected at 12 months post-MI, via the internet portal. These main outcome variables of interest were HADS-T and its respective subscales, followed by the CAQ, MADRS-S and BADS-SF. Along with background and demographic variables, these measures were collected at baseline, end of treatment at 14 weeks and at 12-months post-MI. This study sought to compare only long term data between baseline and the 12-month long-term follow-up, yet results for the post-treatment efficacy can be read elsewhere [72]. This study also obtained data from the Swedish National Board of Health and Welfare on CVD events and mortality covering the period from the first patient inclusion until data extraction. The 10th international classification of disease system (ICD-10) [95] was used for all diagnoses. A CVD event for the purpose of this study, included the following: CVD Death (ICD cause of death code "I"), acute coronary syndrome (ACS) (ICD codes I200, I21 and I22), heart failure (ICD codes I50 and I110), stroke (ICD codes I61, I62, I63 and I64) and revascularisation (codes FNG00, FNG02, FNG05, FNG10 and FNC).

Study design and data analysis

Multiple linear modelling was performed to measure the treatment effect on the primary outcome HADS-T and the subscales HADS-A and HADS-D. Secondary outcomes included the effect of treatment on CAQ, MADRS-S and BADS-SF total scores. Age, sex and baseline levels of the respective outcome were all used as covariates in the models to control for these factors. The intention to treat (ITT) principle was applied meaning that missing values were imputed using multiple imputation via chained equations and predictive mean matching [96]. Complete case and per protocol analyses were conducted as supplementary to the main ITT analyses.

Multivariate cox regression was performed to identify hazard ratios with 95% confidence intervals (CI). Time (in days) to first CVD event was used as the outcome with the exposures as treatment group beginning from the date of randomisation until the date of the event or the censoring date 31st December 2018. For this time-to-event analysis, an event counted as incidence of death

due to cardiovascular cause or other major adverse cardiovascular event (MACE).

Study II

Study aims and research question

The aim was to build from the gained experience of Study I, previous literature and, continuous input and collaboration with patient research partners (PRPs) to develop an internet intervention specifically made for patients experiencing high levels of anxiety or stress following MINOCA or TS.

Study design and participants

Study II applied a participatory action design to the process of developing and creating a novel internet intervention for patients with MINOCA or TS. PRPs were recruited from Södersjukhuset hospital in Stockholm and voluntarily agreed to share their experiences of MINOCA/TS. This initially began with a small group of the PRPs who attended focus group meetings, sharing their experiences and stories with some of the research group. As the stages of the intervention progressed, the involvement of PRPs developed into a collaborative effort whereby they tested material and gave valuable feedback for how to improve upon it. This type of involvement is considered to be "collaboration" according to PPI protocols, which actively involves PRPs in research choices and decisions, as opposed to consultation only [97]. Seven adults, referred to hereon in as patient research partners (PRPs) (five women) with a diagnosis of MINOCA (including TS) participated in the study. The mean age of the group was 58 years and the maximum time since diagnosis was 5 years prior to the study start. Two of the 7 PRPs had a confirmed MINOCA or TS diagnoses whereas the remaining had unspecified MINOCA diagnoses.

Project management

A research team including clinical psychologists, cardiologists, researchers and digital developers were involved in the creation and digitalisation of the intervention. In the beginning, a set of α-priori requirements were agreed upon by the research members. These were used as a starting guide to pinpoint what was or was not feasible (technologically or otherwise) beforehand. Weekly meetings took place once the creation process began in January 2019, and these helped to gather a consensus on both the physical contents of the intervention and the psychological material such as exercises and homework tasks. Five prototype phases were spread over the months that followed, with each phase being made available for the PRPs to test and provide feedback on. This allowed for the next phase to develop with these points and preferences in mind. This iterative approach ensured the intervention was given room for constant improvement and had PRPs concerns pertaining to preference and content at the forefront.

Patient Research Partner involvement

The seven PRPs began involvement in the study through small-scale focus-group discussions (FGD) with three members of the research team: two clinical psychologists responsible for creating the iCBT content (FN and ER) and a cardiac nurse (PL) experienced in working with patients with MINOCA and TS. During these FGDs PRPs spoke about their experiences of life after the diagnosis, as well as areas in which they would need help in regarding clinical care and psychological treatment. The discussions were kept informal and helped form the base of the treatment content along with a brief needs assessment of common problems to be addressed in the iCBT treatment.

PRPs continued to be active in the design of the intervention, as described above, through their participation in providing feedback and through testing the intervention online after each prototype phase. This testing was done through the U-CARE portal, where homework tasks and communication with one of the two psychologists also took place. PRPs were allotted a general time scale of 14-days in which to test the iCBT material and carry out the homework exercises before they were contacted by one of the psychologists to discuss their opinion of the content and provide feedback on the visual design and other areas of concern. The next prototype phase then began and new iCBT material was created as well as adjusting the previous material according to the suggestions of the PRPs, where feasible.

A final meeting with PRPs included a more detailed interview with two members of the research team (EO and SH) where all elements surrounding the design and content of the digital intervention were discussed. As well as this, insight from the PRPs on their views and experiences of being a part of the process (that is, being a patient research partner) were also included in the interview. Following this meeting with the PRPs, two members of the research team (SH and EO) conducted a meeting with three individuals (two clinical psychologists and one cardiologist) that made up what we refer to as the "expert panel". The purpose of this meeting was to gather feedback from clinical researchers with experience of CBT/iCBT interventions or MINOCA/TS patients to further improve the intervention and point out any potential missed areas, given from their area of expertise.

Study III

Aims and research question

Study III aimed to evaluate the feasibility of a full-scale RCT using the developed iCBT intervention and methods from study II.

Design

This feasibility study used a single-arm design meaning that eligible participants were not randomised following inclusion. The design was to test the feasibility of the upcoming *E-health Treatment of Stress and Anxiety in Stockholm Myocardial Infarction with Non-obstructive Coronaries study* (e-SMINC) randomised controlled trial (Clinicaltrials.gov registration identifier: NCT04178434) registered 26th November, 2019. The study design and its methods were based on recommendations from the Consolidated Standards of Reported Trials (CONSORT) statement extension to randomised pilot and feasibility trials [98]. This included a traffic light system that we applied to pre-specified progression criteria that guided whether to proceed (green light), proceed with amendments (yellow light) or major amendments/consider not to proceed (red light) to conduct the full-scale randomised trial [79].

Study recruitment was undertaken at Södersjukhuset hospital in Stockholm, Sweden, and mostly by members of the research team. This enabled direct opportunity for feedback relating to potential issues in the recruitment procedures that may be problematic for the planned RCT.

The U-CARE portal was used for data collection as well as the delivery of the intervention.

Study participants

Participants were screened for eligibility after admission to the coronary care unit (CCU). A verified MINOCA or TS was required for patients to be deemed eligible as well as ≤50% stenosis according to angiography undertaken within one month of the acute event to confirm the diagnosis. Other eligibility criteria included: age between 30 and 80 years and sinus rhythm on electrocardiogram (ECG) at admission. Exclusion criteria were as follows: acute myocarditis, acute pulmonary embolism, acute MI (type II), previous MI due to CAD, cardiomyopathy other than TS, severe kidney disease and severe pulmonary disease. Insufficiency in the Swedish language, lacking access to a computer or the internet, as well as unwillingness to use them were also criteria for exclusion. At stage 2 participants provided signed informed consent before screening for further eligibility criteria which included a score of ≥25 on PSS-14 and/or ≥8 on HADS-A.

Measurements and feasibility criteria

Before discharge from the coronary care unit (CCU), participants completed self-reported questionnaires providing information on demographic variables. This was done as part of the initial screening procedure. Outcome measurements that are intended to detect effectiveness of the treatment (but only used as a tentative assessment in this feasibility study) were administered pre and post-intervention coinciding with 2 and 12 weeks post-discharge from the CCU. Email and SMS reminders were used to prompt participants to complete the questionnaires and, upon this completion, they were granted direct access to the online intervention. Participants were given one week to respond to the initial prompts before being prompted again. Following this, they were contacted by telephone if still unresponsive after one more week. Pre- and post-intervention questionnaires included: PSS-14, HADS-A, Rand-36, CAQ and IES-6.

Participants that had worked actively with the intervention were interviewed over the telephone about their attitudes towards, and experiences of, the treatment. These were recorded and later transcribed for qualitative assessment.

The main feasibility criteria this study aimed to assess concerned feasibility surrounding (a) the recruitment (b) data collection and (c) the intervention. These progression criteria are outlined in Table 3. Some items were pre-specified in terms of the proportion required in order to be given a green, yellow or red light. Other criteria were decided beforehand but had no pre-specified value needed to be met in order to be classified as green, yellow or red lights.

Table 3 Pre-specified progression criteria and research questions posed in study III

	Green Light	Yellow Light	Red Light
Feasibility of recruitment			
Monthly number of patients screened for eligibility at stage 1	>4	2-4	1
Proportion of patients invited among patients screened at stage 1	>50%	25–50%	<25%
Proportion of participants consenting among patients invited	>5%	25–50%	<25%
Proportion of participants found eligible for intervention among patients screened at stage 2	>50%	25–50%	<25%
Main reasons for ineligibility and non-consent			
Average time needed to inform patients and screen for eligibility			
Feasibility of data collection			

Time needed for participants to complete each of the three assessments (screening, pre-intervention, post-intervention)			
Changes in outcome variables between assessments			
Proportion of patients allocated to intervention that normalized their scores on PSS-14 (<25) and HADS-A (<8) at pre- and post-intervention			
Feasibility of intervention			
Proportion of participants that start working in the program (≥1 step) among participants allocated to intervention	>90%	90–60%	<60%
Proportion of participants that completed at least five steps of the intervention among those allocated to intervention	>70%	40–70%	<40%
Proportion of participants that complete post-intervention among those allocated to treatment	>90%	60–90%	<60%
Mean number of steps completed by the participants allocated to the intervention			
Number of reminders sent to encourage patients to start and continue working in the intervention			
Participant experiences of the intervention			
Participant experiences of unwanted distress, including reasons			
Participant experiences of the technical functioning of the portal used for intervention and assessment			
Time needed for psychologists to guide patients in the intervention			

Note Green light: No concerns regarding feasibility and/or acceptance, no need for further analysis or amendments. Yellow light: Possible concerns relating to feasibility and/or acceptance, need for further analysis, minor amendments might be necessary. Red light: Serious indication of low feasibility and/or acceptance, need for further analysis. Major amendments or discontinuation of trial might be necessary. The progression criteria were set to be analysed separately rather than in conjunction. PSS-14 = Perceived Stress Scale, 14-item version; HADS-A = Hospital Anxiety and Depression Scale, Anxiety subscale.

Intervention procedure

The intervention was the same as described and developed in Study II; a nine step internet CBT-based intervention. The first six steps of the intervention were made accessible upon completion of the pre-intervention assessments. Recommended work-through time was one step per week. After step six, participants could activate steps seven and eight, which were optional, or continue directly to step nine which summarised the content and focussed on

maintenance and relapse prevention. It was thus possible to count full adherence as completing either seven or nine steps of the intervention. The intervention was regarded as completed per protocol for participants completing five steps or more.

Data analysis

Quantitative data were analysed and reported descriptively. We used Cohen's *d* with 95% confidence intervals to calculate within-group effect sizes in changes between the pre and post-intervention measurements. Missing data were handled by applying individual mean imputation in cases where ≤20% of data were missing in the scale. This method was based on principles described by Shrive and co-authors [99].

Qualitative data from interviews, free-text responses and researcher logs were summarised and coded into themes using methods inspired by content analysis.

We used A process for Decision-making after Pilot and feasibility Trials (ADePT) [100] to group potential issues raised from the qualitative findings and the progression criteria into three categories depending on whether they were thought to be problematic in the trial only (type A), in both the trial and the real-world setting (type B) or in the real-world setting only (type C). Thereafter the group discussed possible solutions during research meetings and used these to guide amendments.

Study IV

Aims and research questions

Study IV aimed to investigate, in advance of an ongoing registry-based RCT (RRCT), the potential association of β-blocker dose with patient reported HRQoL. We aimed at using data obtained from the Swedish national registers to estimate the association, based on a similar study that did not find that MI patients taking ≥50% the recommended dose of β-blockers had lower risk for recurrent MI or mortality compared to MI patients taking <50% of the recommended β-blocker dose.

Design

The study design was observational and used Swedish national registers to obtain sociodemographic, clinical and medication data as well as self-reported HRQoL as measured by the EQ5D-3L. We utilised the SWEDEHEART RIKS-HIA register which collects >100 variables related to hospital admissions from all CCUs in Sweden for patients admitted with acute coronary syndrome. The ICD-10 was used to identify cases with a diagnosis of MI (ICD-10, I21-I23), as made by the responsible cardiologist during hospitalisation. We utilised the NPR to obtain data on admissions and outpatient visits, and the PDR to obtain data related to prescribed medication. Socioeconomic variables (e.g. birth country, education, income) were obtained from Statistics Sweden (SCB) [101].

The SWEDEHEART SEPHIA register was also used to collect data for the main outcome variables, taken from the first (6-10 week post-MI) and second (12-14 months post-MI) follow-up time points where secondary prevention variables are collected. The EQ5D anxiety/depression domain was dichotomised into a two-level variable Emotional Distress (whereby response 1 = no emotional distress and response 2 or 3 (moderate or severe responses combined) = emotional distress). In this study we were interested in three EQ5D outcomes: (i) EQ5D emotional distress (ii) EQ5D-VAS and (iii) EQ5D Index score (EQ5D-I) at both SEPHIA follow-ups.

Our exposure in this model was β-blocker dose as recorded from the first dispensation post-hospital discharge. Target doses of prescribed β-blockers, as based on previous studies [102–105], were: metoprolol 200 mg/day; bisoprolol 10 mg/day; atenolol 100 mg/day. As defined in previous trials [102,105,106] proportion of pre-defined target dose was dichotomised as: <50% of the target dose and ≥50 % of the target dose. Reference dose was <50% and was the same for all analyses.

Analysis

Main analysis was conducted on first-time MI patients aged 18-74 years old, registered in the SWEDEHEART register, surviving until the second SEPHIA follow-up (12-14 months post-MI) and enrolled in cardiac rehabilitation. We performed secondary sensitivity analyses on (i) predefined subpopulation stratified by sex (male/female) and age (<65 years/65-74 years), (ii) complete case analysis, and (iii) second β-blocker dispensation and reported dosage to ascertain dosage stability (exposure misclassification) by repeating all analyses, but using the dose reported at second dispensation as the main exposure.

Missing data was handled by performing multiple imputation via chained equations and predictive mean matching. Following Rubin's rules we pooled analyses across the five imputed datasets [96,107]. To estimate pooled point estimates with 95% confidence intervals (CIs) we performed crude, and adjusted, linear (for EQ5D-I and EQ5D-VAS outcomes) and logistic (Emotional distress outcome) regression. These included linear main effects and modelled age as a quadratic term in the case of a non-linear relationship with the exposure variable. With the exception of numerical age (which required adjusting for within each age stratum) the variable in question was not adjusted for when performing stratified analyses. Data was pre-processed and analysed using R version 4.0.1 [108].

Covariates

We included covariates based on a directed acyclic graph (not shown). This was to control for measured confounding and to increase the estimated association precision. In-hospital variables included: hospital size (small/medium/large), admission year, admission-to-discharge time, sex, age, smoking status, occupational status, diabetes, body mass index (BMI), hypertension, previous stroke, left ventricular ejection fraction (LVEF), heart rate, systolic blood pressure (SBP), infarction type (ST-elevated/Non-ST elevated MI (STEMI/NSTEMI)), reperfusion and revascularisation. Discharge medications were: ACE inhibitors, angiotensin II receptor blockers (ARB), oral anticoagulation, other antiplatelets, aspirin, calcium channel blockers (CCB), digitalis, diuretics, statins, other lipid lowering agents, nitrates, prior diagnosis of asthma, bronchitis, emphysema, other chronic respiratory disease, peripheral artery disease, depression, and anxiety. Socioeconomic status variables included: country of birth (foreign/Sweden), prior year household income adjusted for family composition (quintiles), and highest attained education (primary/secondary/higher).

Study V

Aims and research question

The aims of Study V were to build from the findings in Study IV in order to present the rationale and trial design including background data from the first 100 patients recruited into a fully controlled RRCT sub-study comparing QoL in patients randomised to β-blocker treatment or no treatment. Study V also aimed to present the strengths and challenges of using digitalised in-hospital data collection methods.

Design

The Randomized Evaluation of Decreased Usage of beta-bloCkErs after myocardial infarction (REDUCE): Quality of Life (RQoL) study is an ongoing, multicentre, prospective, randomised, open, blinded-endpoint sub-study aiming to evaluate the association between β-blockers or no β-blockers and quality of life (QoL) in post-MI patients with normal left ventricular function. The parent study REDUCE (ClinicalTrials.gov identifier NCT03278509) is an RRCT whereby patients are randomised 1:1 in the SWEDEHEART register upon giving formal consent to participate in the trial. Eligibility to participate in RQoL, and β-blocker group allocation is thus dependent on the patient's initial consent to participate in REDUCE.

Data was collected from the first 100 participants to have passed all data collection points and used to report background characteristics and feasibility-related statistics pertaining to the full study.

We used the Standard Protocol Items for Clinical Trials and related documents (SPIRIT) guidelines [109] to guide the reporting of this trial design and feasibility study.

Study participants

Eligibility for the RQoL sub-study was dependent on initial eligibility to participate in the REDUCE parent study, inclusion criteria included: (i) patients ≥18 years (ii) recruited 1-7 days after MI as defined by the universal definition of MI (type 1) and included in the SWEDEHEART registry (iii) coronary angiography undertaken during hospitalisation (iv) stenosis ≥ 50 % as documented by coronary angiography, fractional flow reserve (FFR) ≤ 0.80 or instant wave-free ratio (iFR) ≤ 0.89 in any segment at any time point before randomisation, (v) normal ejection fraction (EF ≥50%) according to echocardiography and (vi) obtained informed written consent. To further be eligible for participation in RQoL the patient was required to be able to read and understand Swedish and provide additional informed consent. Exclusion criteria were the following: (i) any condition that may influence the ability to comply

with the study protocol, (ii) contraindications for β-blockade or (iii) indication for β-blockade other than as secondary prevention according to the treating physician.

Procedure and data collection

Data was collected at three time points and aimed to coincide with the SEPHIA follow-ups: baseline (in-hospital, 1-7 days post-MI), first follow-up (6-10 weeks post-MI) and second follow-up (12-14 months post-MI).

Upon consenting to take part in the study, participants were asked to complete a short battery of questionnaires either via the Portal or using pen and paper. They were informed that their preference for digital or paper methods could be changed at a later stage if desired. Each participant, had a unique study code that was recorded in the study logs by each participating hospital and regularly uploaded to a secure data-sharing vault where the research team in Uppsala could access the study logs and oversee the recruitment in a general study log. This was to keep track of all participants in the study, when and if they needed to be sent out paper questionnaires and/or be reminded by telephone to do so.

Background data and informed consent was collected in hospital, unless the patient had been sent home prior to completing the questionnaires, in which case they could fill these in at home within 7 days of the MI onset. The baseline measures included: background questions, HADS questionnaire, CAQ, WHO-5, ASEX questionnaire and the BMQ. These were completed on the Portal, using BankID login authentication or username and password, or on paper. Paper questionnaires held the benefit of being a viable option for patients with preference for non-digital questionnaires, and also in the event of technical problems or hospital staff being short on time. Paper questionnaires were then entered manually into the Portal by research staff, giving each participant a unique participant portal ID and even making it possible for switching to digital methods at follow-up. Both the 6-10 weeks and 12-14 months follow-ups were completed by patients at home and administered by research staff in Uppsala. With the exception of the BMQ, questionnaires were the same across all data collection time points. At both follow-up occasions participants were asked to report if they are currently taking β-blockers and, if so, any self-reported side effects they have experienced. A general overview of the study process is shown in Figure 1 below.

Figure 1 Timeline and flowchart showing the study data collection points post-myocardial infarction (MI)

For the purpose of this design and feasibility paper, we used data from the first 100 participants enrolled in RQoL to assess the study process and functionality. Data was extracted from the Portal for all questionnaires across the three data collection points. Other data including demographic, background and medical information were taken from the SWEDEHEART registers and from the study logs filled in by hospital staff. The EQ5D, routinely collected for all patients in the SEPHIA register, will be utilised in the planned RCT's analysis as an outcome of interest measuring HRQoL, and was not included in this study.

Results and findings

Study I

Primary outcomes

Analysis of the HADS-T scores at 1 year post-MI found no difference in the effect of iCBT on HADS-T between the treatment and control group (β = -1.14, 95% CI -2.73 to 0.45, *P*=0.16). Sensitivity analysis with observed data showed no effect of treatment on the primary outcome of HADS-T (β = -1.3, 95% CI -2.96 to 0.27, *P*=.10) and this effect was not found in the per protocol supplementary analysis either (β = -1.3, 95% CI -2.90 to 0.41, *P*=.14).

Secondary outcomes

Of the secondary outcomes, the CAQ was the only psychological assessment to show a significant effect of treatment (β = -2.58, 95% CI -4.75 to 0.42, *P*=.02). Figure 2 presents the mean scores of the primary and secondary outcomes across three time points (baseline, post-treatment and 1 year post-MI follow-up).

Table 4 shows model estimates from the primary and secondary outcomes across both groups at baseline, post-treatment and 12-month follow-up.

CVD clinical outcomes

Thirty six participants (31%) in the iCBT treatment group and 25 (20%) in the control group had at least one incidence of MACE or fatal CVD. Time to event estimates using Cox regression [HR (95% CI)] revealed that patients in the treatment group had a numerically greater risk of the composite endpoint which included incidence of cardiovascular death or MACE, although this was not statistically significant [1.8 (0.96 - 3.4, *P*=.07)]. Post-hoc analysis which adjusted for previous MI and diabetes attenuated this risk [1.5 (0.8 - 2.8, *P*= 0.25)].

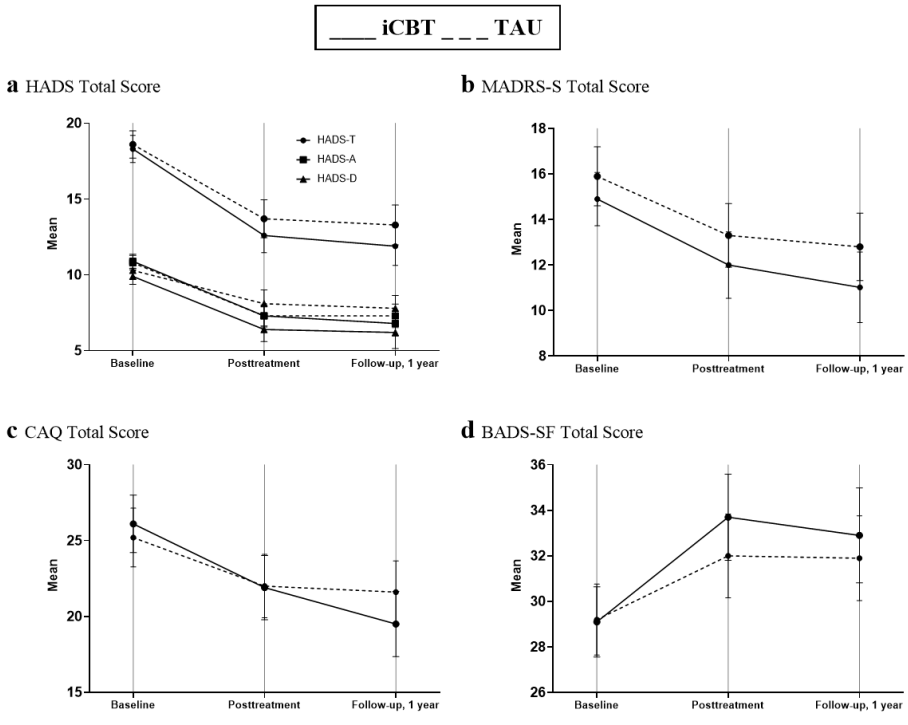


Figure 2 Mean scores of the primary and secondary psychological symptom outcomes across three time points (baseline, post-treatment and 1 year post-MI follow-up). HADS, Hospital Anxiety and Depression Scale; MADRS-S, Montgomery Åsberg Depression Rating Scale Self-Rated; CAQ, Cardiac Anxiety Questionnaire; BADS-SF, Behavioural Activation for Depression Scale Short-Form

Note. A decrease in the direction of total scores for HADS, MADRS-S and CAQ denote improvement in symptoms. An increase in total score for BADS-SF implies a higher activation of change in depression-related behaviours and is thus denotes a positive improvement.

Table 4 Outcomes at baseline, post-treatment and 12-month follow-up, mean change and treatment effects. Mean (SD) and change are calculated from observed data. Estimate of effect (beta) are pooled adjusted coefficients for treatment versus control on imputed data. Outcome measures at post-treatment and 12-month follow-up are adjusted for age, sex and baseline score on each outcome, respectively. Treatment refers to the group receiving internet-based cognitive behavioral therapy (iCBT); Control refers to treatment as usual (TAU).

Outcome	Baseline, mean (SD)	Post-treatment, mean (SD)	12-month follow-up, mean (SD)	Change (baseline to follow-up)	Effect, Beta (95% CI)	P
HADS-T						
Treatment	18.3 (4.9)	12.6 (5.6)	11.9 (6)	-6.4	-1.14 (-2.73, 0.45)	0.16
Control	18.6 (5.0)	13.7 (6.8)	13.3 (7)	-5.3		
HADS-A						
Treatment	10.9 (2.4)	7.3 (3.1)	6.8 (3.7)	-4.1	-0.64 (-1.65, 0.37)	0.21
Control	10.8 (2.5)	7.3 (3.7)	7.3 (3.9)	-3.5		
HADS-D						
Treatment	9.9 (2.2)	6.4 (3.0)	6.2 (3.8)	-3.7	-1.08 (-2.31, 0.16)	0.09
Control	10.3 (2.5)	8.1 (3.8)	7.8 (3.5)	-2.5		
MADRS-S						
Treatment	14.9 (6.4)	12.0 (7.2)	11. (7.2)	-3.9	-1.03 (-2.83, 0.78)	0.26
Control	15.9 (7.2)	13.3 (7.6)	12.8 (7.9)	-3.1		
CAQ						
Treatment	26.1 (10.3)	21.9 (10.4)	19.5 (10.1)	-6.6	-2.58 (-4.75, -0.42)	0.02
Control	25.2 (10.8)	22.0 (11.3)	21.6 (11)	-3.6		
BADS-SF						
Treatment	29.1 (8.4)	33.7 (9.2)	32.9 (9.5)	3.8	0.64 (-1.67, 2.95)	0.59
Control	29.2 (8.7)	32.0 (9.9)	31.9 (9.8)	2.7		

Study II

Intervention outcome

The resulting intervention was a 9-step psychological treatment for patients with MINOCA and TS, delivered digitally. These steps included: (1) Introduction, (2) Stressors and Stress Behaviors, (3) Stress-specific Self-monitoring, (4) Recovery and Relaxation, (5) Personal Values, (6) Fear and Avoidance, (7) Exposure, (8) Exposure (continued), and (9) Conclusions and Relapse Prevention. Step 7 and 8 are intended as optional steps depending on the personal preference of the participant. Figure 3 shows the steps of the intervention. The recommended work pace was intended for participants to work through one step per week, allowing between 2 to 3 hours per step. In addition to these steps, the intervention included video clips and interviews (with members of the research team including one PRP) as well as information about MINOCA/TS and common psychological reactions after experiencing them.

Views of the intervention

Findings were derived from the final interview with PRPs and covered the content, platform design and personal views of the intervention. Feedback in this discussion for example, lead to step 6 - which was also intended as an optional module due to low participant activity during testing - being made mandatory on the advice of the PRPs who felt that it is was helpful and could be beneficial for future users. The comments and input also lead to extra visual adjustments to the intervention, as well as to additional video content being added.

Terminology was also discussed, such as the use of pronouns, as well as the term “MINOCA” versus “cardiac event” or Takotsubo. It was finally agreed that MINOCA was the preferred term since it encompasses a wide range of classifications including TS (which was the expert consensus at the time, however with the release of the new guidelines is no longer the case). In addition, PRPs disagreed with the term “broken heart syndrome” and its use in medical or non-medical settings, expressing that it was not appropriate and even “glamorised” the condition.

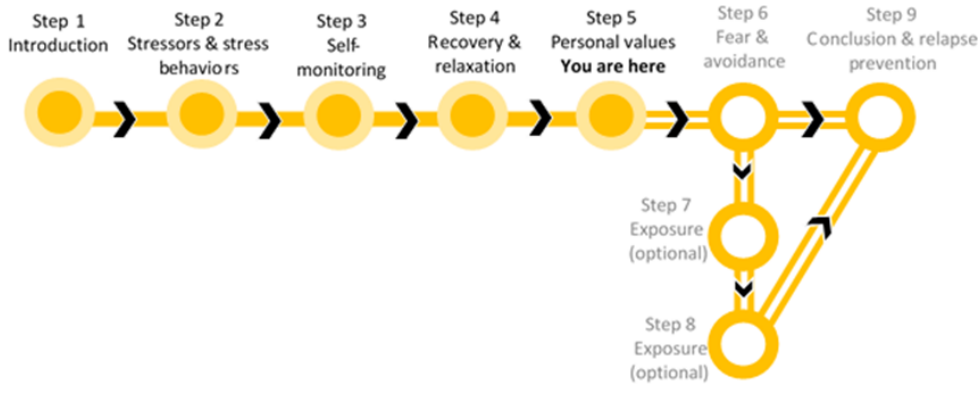


Figure 3 An overview of the intervention showing the possible alternatives for completing a total of 7 or 9 steps

Study III

Study III recruitment took place between December 2019 and April 2021. It took hospital personnel approximately 90 minutes to inform and assess eligibility. In total, 49 patients were screened for eligibility and 18 of those were excluded as not meeting eligibility criteria. Thus, 31 patients were invited to take part in the study, of which 26 consented to the study and were screened for symptoms of anxiety and stress using the HADS-A and PSS-14 instruments. After screening, 12 scored below the threshold score for inclusion on the PSS-14 and/or HADS-A, and 14 participants scored above the threshold on either and were thus eligible. Of these 14 participants, two did not complete the pre-intervention questionnaires, and one withdrew consent prior to starting the intervention. Swedish was not the native language of any of these participants. In total, 11 participants were thus included into the study and offered the intervention.

The mean age of the included participants was 64.3 years and 9 out of 11 were female. TS was the most common diagnosis (7 out of 11) while the remaining were diagnosed with MINOCA (4 out of 11). Cohen's *d* effect sizes between pre- and post-intervention were large (HADS-A: $d = 1.0$; PSS: $d = 1.5$). Six out of 8 (1 missing) and 6 out of 9 normalised their scores on PSS-14 (<25) and HADS-A (<8), respectively.

Intervention

Ten of the 11 participants started working on the intervention, and one withdrew after completing the first step (citing complications due to another medical condition). The pre-defined goal of five steps was reached by all nine of the remaining participants and the mean number of completed steps was 6.9. One participant activated and completed the optional steps, with a focus on heart-related fear.

In terms of time and resources used by the psychologists, reminders sent were: (i) an average of 1.0 reminder to complete the first intervention (ii) an average of 2.2 reminders due to inactivity (iii) a total of 3 reminders to inform the participant of unread feedback/messages. A total mean time of approximately 285 minutes was spent for standard patients completing steps one to six, plus nine. The need to manually activate steps seven and eight appeared to discourage participants from continuing further.

Interviews

Interview topics covered several areas related to the intervention and overall experience. These covered: (i) format (ii) material and content (iii) psychologist contact and (iv) technical functioning. Feedback on homework tasks and contact with the psychologist were reported as being important factors in the overall positive experience of the treatment. Much of the content (e.g. material and steps that focussed on stress) were seen as relevant and examples helped clarify concepts. Negative feedback referred mostly to the time and concentration needed to complete the written tasks which could become stressful.

Feasibility criteria

Of the pre-specified progression criteria, all but two were within the highest (green) category meaning that there were no concerns for the planned RCT in these areas. The number of patients screened monthly (Q1) and the proportion completing the post-intervention questionnaires (Q12) was in the mid (yellow) category, indicating an area for possible concerns with possible minor amendments required.

Table 5 Pre-specified progression criteria with the respective number/percentages required under each colour category followed by the observed values recorded in the present study

		Green	Yellow	Red	Observed
Q1.	Monthly patients screened for eligibility at stage 1	<4	2–4	1	49/16=3.06
Q2.	Proportion of patients invited among patients screened at stage 1	<50%	25–50%	<25%	31/49=63%
Q3.	Proportion of participants consenting among patients invited	<50%	25–50%	<25%	26/31=84%
Q4.	Proportion of participants found eligible for intervention among patients screened at stage 2	<50%	25–50%	<25%	14/26=54%
Q10.	Proportion of participants that start working in the program (≥ 1 step) among participants allocated to intervention	<90%	60–90%	<60%	10/11=91%
Q11.	Proportion of participants that completed at least five steps of the intervention among those allocated to intervention	<70%	40–70%	<40%	9/11=82%
Q12.	Proportion of participants that complete the post-intervention questionnaire among those allocated to treatment	<90%	60–90%	<60%	9/11=82%

Note. The progression criteria were set to be analysed separately rather than in conjunction.

Study IV

We reported a total study population that included 35612 first-time MI patients, aged 18-75 years, discharged with β-blockers, surviving until the second SEPHIA follow-up and enrolled in cardiac rehabilitation. Of these patients, 24082 (67.6%) were dispensed prescriptions with <50 % of the target β-blocker dose and 11530 (32.4%) with ≥50% of the target β-blocker dose.

Patients reported a median EQ5D-I of 0.84 [0.72, 1.00], EQ5D-VAS of 75 [60, 85] and 13563 (38.1%) reported emotional distress at the first follow-up, 6-10 weeks post-MI. A slightly higher EQ5D-VAS (median of 80 [65, 90]), and a smaller percentage reporting emotional distress (10090 (32.9%)) was seen at the second, 12-14 month follow-up.

Descriptive statistical analysis showed that patients taking <50% of the target dose were less likely to have diabetes, previous stroke or hypertension, higher systolic blood pressure and were more likely to have a shorter hospital stay than those taking ≥50% of the target dose. A higher education level, full-

time employment and higher income were also more likely in the group taking <50% of the target β-blocker dose.

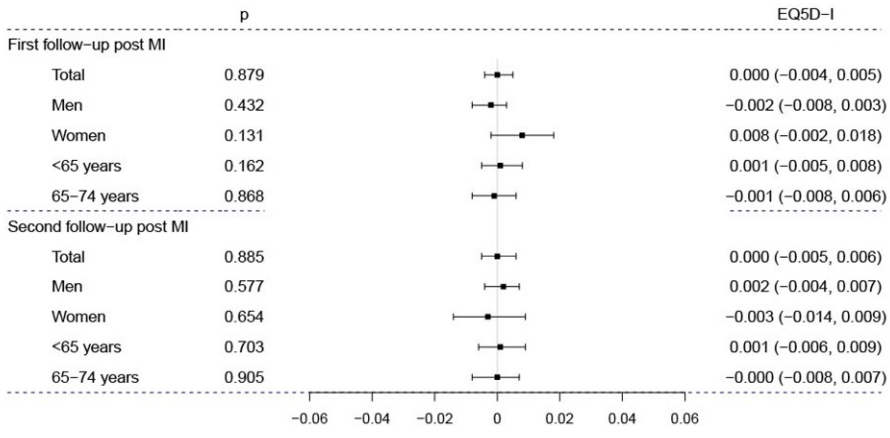
Main analysis

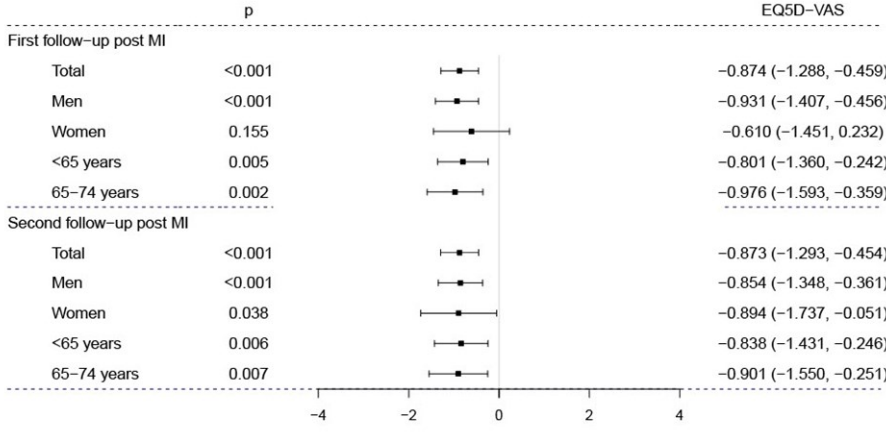
Of the three EQ5D outcomes in the total population at both follow-up time points, only the EQ5D-VAS was significantly lower in the group taking ≥50% of the target β-blocker dose (-0.87 [-1.23, -0.46], $P<.001$) after adjustment for predefined covariates. Findings were similar across all population strata, with the exception of the sub-group analysis on women, which was only significant at the second follow-up, but not the first. The EQ5D-I and EQ5D Emotional Distress showed no differences across β-blocker dose group at either follow-up time points. Stratified analyses at both follow-ups are shown in Figure 4.

Sensitivity analysis

Complete case analysis for the total population did not differ from the main analysis. Of all outcomes, only the EQ5D-VAS was significantly lower for those taking ≥50% of the target β-blocker dose at the second follow-up (-0.638 [-1.207, -0.068] $P<0.05$.

Results from the analysis of the second dispensation did not differ substantially from the main analysis.


p
EQ5D−I
First follow−up post MI
Total 0.879 0.000 (−0.004, 0.005)
Men 0.432 −0.002 (−0.008, 0.003)
Women 0.131 0.008 (−0.002, 0.018)
<65 years 0.162 0.001 (−0.005, 0.008)
65−74 years 0.868 −0.001 (−0.008, 0.006)
Second follow−up post MI
Total 0.885 0.000 (−0.005, 0.006)
Men 0.577 0.002 (−0.004, 0.007)
Women 0.654 −0.003 (−0.014, 0.009)
<65 years 0.703 0.001 (−0.006, 0.009)
65−74 years 0.905 −0.000 (−0.008, 0.007)
−0.06 −0.04 −0.02 0 0.02 0.04 0.06


p
EQ5D−VAS
First follow−up post MI
Total <0.001 −0.874 (−1.288, −0.459)
Men <0.001 −0.931 (−1.407, −0.456)
Women 0.155 −0.610 (−1.451, 0.232)
<65 years 0.005 −0.801 (−1.360, −0.242)
65−74 years 0.002 −0.976 (−1.593, −0.359)
Second follow−up post MI
Total <0.001 −0.873 (−1.293, −0.454)
Men <0.001 −0.854 (−1.348, −0.361)
Women 0.038 −0.894 (−1.737, −0.051)
<65 years 0.006 −0.838 (−1.431, −0.246)
65−74 years 0.007 −0.901 (−1.550, −0.251)
−4 −2 0 2 4

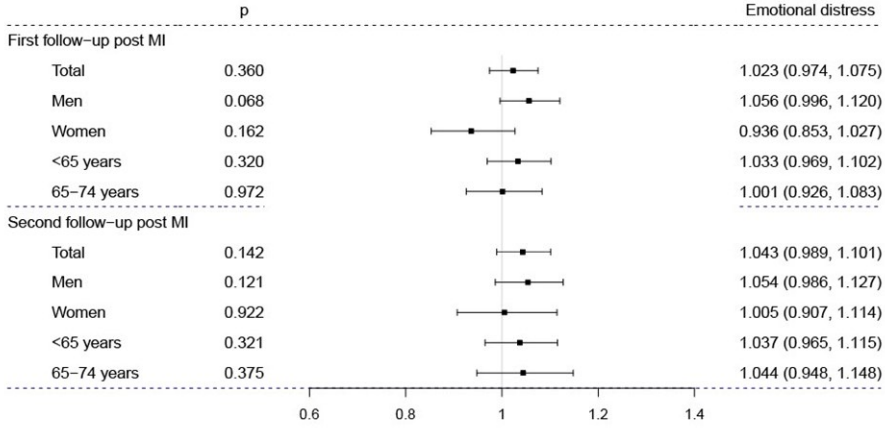

p
Emotional distress
First follow−up post MI
Total 0.360 1.023 (0.974, 1.075)
Men 0.068 1.056 (0.996, 1.120)
Women 0.162 0.936 (0.853, 1.027)
<65 years 0.320 1.033 (0.969, 1.102)
65−74 years 0.972 1.001 (0.926, 1.083)
Second follow−up post MI
Total 0.142 1.043 (0.989, 1.101)
Men 0.121 1.054 (0.986, 1.127)
Women 0.922 1.005 (0.907, 1.114)
<65 years 0.321 1.037 (0.965, 1.115)
65−74 years 0.375 1.044 (0.948, 1.148)
0.6 0.8 1 1.2 1.4

Figure 4 Adjusted main analysis of <50% of the target β-blocker dose (reference) vs ≥50% of the target dose for the three EQ5D outcomes as separated by follow-up time. Data shown are point estimates and 95% confidence intervals (CIs). P-values are from pooled linear (EQ5D-I and EQ5D-VAS) or logistic (Emotional distress) regression model estimates following multiple imputation and multivariable adjustment. Dose refers to the first post-discharge dispensation of β-blocker. Reference group was patients receiving <50% target β-blocker reference dose. EQ5D-I, index calculated using the EQ5D item responses; EQ5D-VAS, Visual Analogue Scale, 0-100 numeric self-rating of a patient's present general health (100 = best imaginable health state); Emotional distress, equal to response levels 2 or 3 on the EQ5D Anxiety/Depression item indicating presence of general psychological distress.

Study V

Recruitment of the first 100 patients was carried out across four hospitals in Sweden and took approximately 10 months. As of December 2021, and since study conception in July 2018, a total of 721 patients were recruited. Figure 5 shows the cumulative and the predicted total recruited patients by study completion.

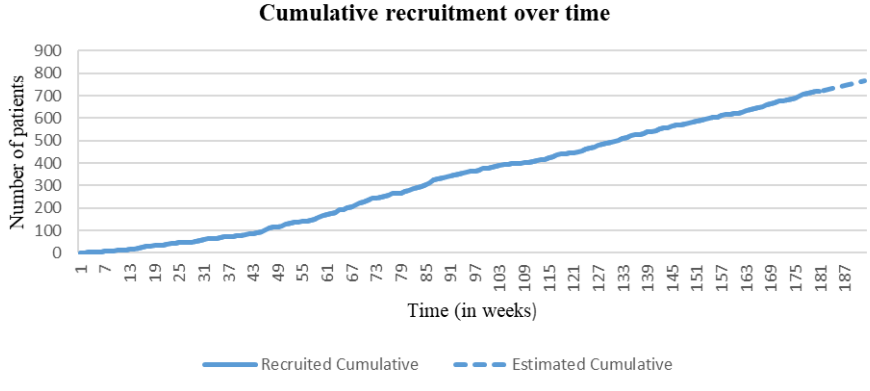


Figure 5 Total cumulative and predicted number of patients recruited into the study since July 2018 until anticipated study conclusion

Data from the first 100 participants shows that retention in the study was good across both follow-ups, but expectedly, dropped over time. At the first follow-up, 93% had completed the questionnaires, compared to 81% at the second follow-up. The participants had a mean age of 64.4 years and 80% were male. Overall, the two groups appeared to be well-balanced after randomisation according to background data and characteristics shown in Table 6. One patient died between the first and second follow-up. Telephone call reminders worked well, especially at the first follow-up where 25 of 29 participants completed

the questionnaires after receiving a reminder call. This dropped to 20 out of 30 reminded at second follow-up.

Table 6 Background demographic information of the first 100 patients recruited into the RQoL study, divided by treatment group

	Total, N	β-blocker, N (%)	No β-blocker, N (%)	Missing data, N
Randomization group	**100**	**45**	**55**	
Baseline				2
Digital format	50 (51)	24 (24.5)	26 (26.5)	
Paper format	48 (49)	21 (21.4)	27 (27.6)	
Mean days between MI and baseline	1.6 days	1.8 days	1.4 days	
Min and max days between MI and baseline	0-7 days	0-6 days	0-7 days	
HADS-A	5.9	6.5	5.4	2
HADS-D	3.8	3.8	3.8	3
CAQ total score	20.7	19.6	21.7	8
WHO-5 total score	62.2	63.2	61.3	2
ASEX total score*	10.9	11.4	10.7	7
Follow-up 1				
Total number responding	93	45	48	
Digital format	56 (60)	29 (31)	27 (29)	
Paper format	37 (40)	16 (17)	21 (23)	
Number reminded (of which responded)	25 (27)	8 (9)	17 (19)	
Number reminded (total)	29 (30)	8 (9)	21 (23)	
Not responded	3	0 (0)	3 (3)	
Declined further participation	4 (4)	0 (0)	4 (4)	
Mean days between prompt and OP completion	6.7 days	5.7 days	7.7 days	
Minimum number of days	0	0	0	
Maximum number of days	30	23	30	
Follow-up 2				
Number responding (total)	80 (81)	38 (40)	42 (44)	
Digital format	49 (61)	26 (32.5)	23 (28.5)	
Paper format	31 (39)	12 (15)	19 (24)	
Number reminded (of which responded)	20 (25)	9 (11)	11 (14)	

Number reminded (total)	30 (31.6)	13 (13.7)	17 (17.9)
Not responded	13 (13.7)	6 (6.3)	7 (7.4)
Declined participation	2 (2)	0 (0)	2 (2)
Deceased	1 (1)	1 (1)	0 (0)
Mean days between prompt and OP completion	6	5.3	6.5
Minimum number of days	0	0	0
Maximum number of days	28	19	28

*Items 1-3. HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS anxiety subscale; HADS-D, HADS depression subscale; CAQ, Cardiac Anxiety Questionnaire; WHO-5, World Health Organization Wellbeing 5 Scale; ASEX, Arizona Sexual Experiences Scale

Discussion

Treatment attrition in e-Health interventions

As is often the case in e-health intervention research, attrition to treatment is a major problem and many trials report that participants do not adhere to the majority of the steps in the treatment programme [63,110]. This was particularly the case with the U-CARE Heart trial [72] and for a similar internet-based depression treatment for people with CAD [111]. Female sex and higher self-rated cardiac anxiety were two variables associated with lower dropout (higher adherence) in the U-CARE Heart trial [112]. Further findings from a qualitative study of patients' experiences of taking part in internet-based CBT for generalised anxiety found that several overlapping factors related to (i) the patient's perception of the treatment and (ii) the patient's situation, contributed to early termination of the treatment [64]. Only 53.8% of those allocated to the iCBT group in Study I completed the introductory module and the majority of those that did complete the introduction did not proceed further with the intervention. A subsequent mixed-methods study investigating reasons for the non-adherence as well as participants' views of the intervention revealed that many thought the treatment was too burdensome, long and strenuous [113]. Suggestions for improvements covered a wide range of categories including changes to the portal, the treatment programme, therapist communication and functional features. In study II, we hoped to use these findings to avoid similar problems with patient dissatisfaction and attrition. We also conducted a comprehensive, patient-involved process that utilised the principles of PPI to ensure we gathered as much input from MINOCA and TS patients as possible. Whilst we cannot be sure this will solve the problems experienced in Study I, we believe the input of PRPs will ensure the intervention is suitable and relevant to the intended users.

Are digital methods always suitable?

Digital interventions offer many benefits over more traditional forms and are usually praised for their accessibility and cost-effectiveness [54,55]. However as noted in study III, they can be perceived as demanding and unsuitable for certain participants, particularly those with concentration or reading difficulties (such as people with a diagnosis of attention deficit hyperactivity disorder

(ADHD) or dyslexia), sight problems or computer illiteracy. These individuals may benefit from a more traditional face-to-face therapeutic setting. Since age is also a major risk factor for MI [114], many patients with MI or CVD recruited into internet-based intervention studies are expectedly older on average than other patient groups and may feel more anxious about using digital technology [115]. Providing training to these participants in how to use the technology associated with the intervention and offering accessible devices could improve older people's confidence in their ability to utilise digital interventions [116].

Limited language comprehension can also be a contributing factor to the uptake of iCBT interventions and may have been a relevant consideration for study III. When we evaluated the flow of participants we noticed some had been excluded between screening and pre-intervention (n=3) due to incomplete questionnaires or withdrawal of consent. This did not impact the feasibility progression criteria for the rate of participants screened to those allocated to treatment. However, it did come to the research team's attention, upon reviewing the data descriptively, that these three participants were born outside of Sweden and did not have Swedish as their native language. This could have implications for the study's applicability to non-Swedish participants who have Swedish as a second, or even third, language. People who have immigrated to another country utilise mental health or e-health services less than native speakers [117] and are often more difficult to recruit into iCBT-based studies than their native-speaker counterparts [118], although this can be dependent on level of achieved education [119]. Thus, providing the intervention from Study II and III in another language, such as English or Arabic, could prove useful as it has been shown to be a promising treatment approach for similar iCBT treatment in Sweden [120].

Overall, the use of iCBT or internet-based digital collection methods are regarded highly and hold many benefits compared with traditional forms of therapy or data collection methods. While it may not be possible to offer alternative methods to iCBT on most occasions, alternative forms of data collection such as paper questionnaires offered in Study V can be suitable substitutes.

Study specific discussion

Study I:

Few studies investigating the effectiveness of iCBT report long-term outcomes of randomised trials. This can be problematic particularly as spontaneous improvement in emotional distress is sometimes seen in MI patients who were report high emotional distress 2-months post-MI, but not after 12 months [27]. Without studies conducting a longer term follow-up, it cannot be ruled

out that this type of pattern of improvement might emerge without treatment. In addition, previous research has found a long-term difference between groups receiving CBT or CAU in clinical outcomes (such as CVD or recurrent acute MI) where no differences in risk were initially present following treatment [29,121]. This type of result could encourage the possibility of long-term follow-up to investigate differences over time. The U-CARE Heart trial [72] found no post-treatment effects of treatment on the primary or even secondary outcomes, and Study I sought to explore these at 12-months post-MI, as well as compare the differences in risk of CVD and other cardiovascular health measures between the groups on a long-term scale. We did not find a significant effect of treatment on the primary outcome HADS-T or on the clinical outcomes for CVD, but an effect of treatment on CAQ was found.

A similar Italian study likewise did not find a statistical difference in clinical outcomes regarding adverse cardiac events at a three-month follow-up in a CBT treatment group compared to control [48]. The treatment group rather like in study I, had more adverse cardiac events than the control group, although this was not statistically significant either. Furthermore, a qualitative study of iCBT participants' experiences of non-adherence to an internet-delivered programme revealed that some participants experienced negative effects of internet therapy on existing or prior symptoms, triggered by stressful aspects of the treatment [64].

Despite several meta-analyses having reported a positive effect of treatment on both CVD outcomes or CVD-related mortality [49,51,122,123] Study I did not observe this effect. However, the low number of events in the iCBT treatment versus control group (36 vs 25 events) meant that the power of the study was too limited to indicate that there was no effect at all. Furthermore, one must be careful when interpreting the pooled findings from a meta-analysis as these are often only small effects.

Results from study I were to some extent in line with previous trials investigating the effect of psychological therapies on cardiovascular outcomes or mortality. A meta-analysis of CBT interventions for patients with CVD reported positive effects of treatment on symptoms of anxiety and depression, but not on CVD events [124]. The ENRICHD trial offered individuals with depression following MI a course of CBT whilst the SADHEART trial treated depressed MI patients with an antidepressant (Sertraline) and neither study found an effect on cardiac measures or event-free survival [125,126]. However, these trials only measured depression, which in some cases, compared to anxiety, is not as pronounced in those with MI when compared to a reference population [65]. Moreover, both trials initiated therapy less that one month after the index MI, which has since been suggested is too short to be associated with benefits in mortality [51].

Overall, findings from Study I have both been in-line with *and* contrary to similar trials and related studies of iCBT treatment in patients with CVD or related cardiac illness. Due to the low number that adhered to the treatment

beyond the introductory step, it is difficult to infer whether the treatment contributed towards any suggested effect or non-effect. In large, this motivated many of the reasons behind the chosen processes and steps taken in Study II and Study III.

Study II

Many current, novel, internet interventions, particularly those aimed at cardiac populations, do not publish the process or development work involved in creating and producing such an intervention. Many even lack published descriptive content of the theoretical-basis making it difficult to know what content pre-existing studies have included and what components of the intervention are the most effective [123]. Through documenting the process and work involved in Study II, we sought to contribute our documented findings and the process involved in designing a novel, iCBT-based intervention aimed at patients with MINOCA or TS. Work with PRPs lead to several findings that could even be utilised in a wider context, for example in hospital settings. The term "broken heart syndrome", often used as the equivalent term to TS for instance, was not the preferred choice by the PRPs who expressed discomfort with the term for various given reasons, supporting a qualitative study's similar findings about the preferred appropriate terminology of TS patients [127]. Yet, many healthcare professionals still use the term in the present day and are largely unaware of the preferences of TS patients. While this is only a small finding that was intended mainly for applying to the intervention itself, it is a good example of how collaborating with patients enables researchers to understand beyond the current literature and their own preconceptions of the problem.

Although PAR has been increasingly viewed as a valuable method in recent years, room for improving exists, particularly for research involving older adults, who are often underrepresented in PAR research [128,129]. This can be particularly problematic in the field of cardiovascular research where many of the patients involved are aged >60 years. Thus, involving patients in research and decision processes are important for the relevancy of the patient group. The involvement of PRPs in Study II was pivotal to the development of the intervention, making it hopefully relevant, suitable and effective for similar patients with psychological distress following MINOCA or TS.

However, the act of involving PRPs in research does not always guarantee that all needs of the target group can be met. While the team always tried to take the requests and feedback of PRPs into account, this was not always possible, particularly when there were digital constraints or the PRPs suggested in-person psychologist contact which was out of the scope of the study to provide.

A future improvement that could help overcome some of these limitations would perhaps be to individualise the treatment where possible. The current

intervention allows for the user to choose whether or not take the optional heart-related fear modules, and while this appears to be a good start towards customising the programme for the individual, there is some room for improvement.

Study III:

A major goal of study III was to assess the feasibility, practicality and effectiveness of conducting an RCT using the methods described in the study protocol and the intervention developed in Study II. We reported that compliance to the treatment was good and feasibility criteria were met, indicating strong support for the transition to an RCT with minimal cause for concern or need for changes.

Although it is difficult to confirm, the involvement of PRPs in Study II likely contributed towards the successful fulfilment of progression criteria, namely aspects related to the intervention (content, exercises, text etc.) and the study process.

The lower rate of screening compared to the other feasibility criteria reflected that minor revisions were needed to be applied to the protocol. Of these changes, the team decided to increase the number of recruiting hospitals in the RCT to include other hospitals in the Stockholm region. Some weight of the lower screening rate was given to the role that the Covid-19 pandemic played in the functioning of clinical studies, particularly as advice regarding hospital visits was altered to reflect minimal unnecessary contact. Besides this, the need for on-site screening and a verified diagnosis of MINOCA or TS with ECG sinus rhythm at admission and <50% stenosis according to angiography within one month of the acute event, meant that self-referral was not entirely possible for this study. This could have affected the recruitment rate since it is thought that problems with low adherence and treatment activity (as in Study I) could be attributed in part due to the recruitment technique of including patients directly from the hospital. Trials that have utilised other recruitment methods, such as open community recruitment have had some success in comparison to clinical service recruitment [130]. However, despite employing various recruitment strategies that are believed to decrease study attrition, some studies have still struggled with drop-out and in some cases not proceeded to a full trial because of this [111]. Therefore, the team believe that the recruitment strategy in Study III, with the addition of more recruitment hospital sites, is justified and should not be a problem in this regard.

Additional findings from this study contributed to amendments in the RCT protocol. These included adding an additional phone call after the third step and removing the need for activating steps seven and eight, but still having them as optional steps. The decision for changing these were not based on prespecified progression criteria, but instead from participant feedback and eval-

uation of programme behavioural patterns, such as those noticed by the psychologists during treatment. Although the results from the effect of the intervention cannot be inferred by the feasibility study, identifying potential weaknesses and piloting the design will hopefully decrease the chances of running into similar problems in the RCT and support the general use of feasibility and pilot-testing studies prior to commencing an RCT.

Study IV:

The many strengths of using data from registers include the ability to comprise a larger sample than standard observational designs due to the vast range of variables available. This enables good controlling for confounders. In study IV, we used the national Swedish registers including SWEDEHEART registers SEPHIA and RIKS-HIA, the NPR and the PDR to investigate the association of β-blocker dose on HRQoL. Due to the vast amount of data available in these registers we could control for many potential confounders that might lead to contraindications for β-blockers and may have affected the investigated relationship. Using β-blocker dose as the exposure variable can make the results and interpretation susceptible to confounding by indication because some patients are prescribed low or high doses for medical reasons, potentially confounding the relationship with HRQoL if these reasons also correlate with the outcome. Thus, the most robust method of comparing the relationship between β-blockers and the association with multiple outcomes related to QoL (such as HRQoL, symptoms of anxiety and depression, sexual functioning and overall wellbeing) is in a randomised, controlled study such as Study V.

With using the registers to measure the outcome of interest, that is HRQoL, there is of course a limitation as to both the quality and availability of data one can obtain from such registers. We used the EQ5D-3L and its components as a representative measurement of HRQoL. The EQ5D-3L has been supported as a valid instrument for HRQoL in cardiovascular diseases [131,132]. HRQoL has been described as one of three domains of health status and often as the 'perception of the discrepancy between actual and desired functional status' and 'overall impact of disease on well-being' [133]. However, the definition of HRQoL has been labelled ambiguous and its use in literature deemed inconsistent, with instruments often measuring self-perceived health status instead and not always clearly able to distinguish from QoL [134]. Other instruments measuring HRQoL in cardiovascular patient groups have also been validated [135–137] some of which distinguish between generic and illness-specific QoL [138], but these are not used in the SEPHIA register to enable comparison.

Although the EQ5D's ability to measure psychometric properties outside of HRQoL is less favourable than extensive, standardised questionnaires such as those we used in study V, it has the benefit of being quick to administer and can be used across different countries and age groups [88]. The EQ5D has

been the only tool measuring HRQoL in the SWEDEHEART registers. This changed however with the addition of the Patient Health Questionnaire for Depression and Anxiety (the PHQ-4) [139] in 2021, which contains four brief questions on self-reported anxiety and depression.

Study V:

Something that often comes up regarding research into psychosomatic disease and the association with adverse mental health outcomes is the direction of the relationship, the so-called chicken and egg debate. The relationship is rather complex; mental illness is associated with cardiovascular events and vice versa [140–142], but is also associated with higher risk for new events following a cardiovascular event [27,143], it is not clear which may be the more important factor to consider in tailoring treatments. In Study IV, we did not find a direct association between β-blocker dose and HRQoL but we do not know the potential effects when comparing treatment vs no treatment at all as in Study V. In this case, the relationship may also be more complex than simply suggesting that β-blockers are associated with higher or lower HRQoL since there are many factors to consider that may also mediate this relationship. A moral question can also be posed if we are to consider the implications of prescribing β-blockers if they are reported to have a negative effect on one aspect of health (cardiovascular or mental), but no effect on the other. This scenario would be further complicated if the effect is even perhaps protective to cardiovascular or mental health, but detrimental to the other. One assumes that medical guidelines would favour the role that β-blockers play on cardiovascular health over mental health when assessing the necessity of their use in patients with normal heart function (e.g. LVEF > 50%).

Study V used the hospital logs to inform the status of the randomisation group and additionally verified this group allocation with the data provided by SWEDEHEART. Self-reported status on β-blocker consumption and subsequent self-perceived side effects were questions added to the study questionnaires at first and second follow-up. This was largely to gauge the amount of expected crossovers in the planned future analysis, i.e. patients who were randomised to one group, but during the study have since switched or stopped taking their medication, with or without medical consultation. Such crossovers that are not controlled for, could affect the analysis of results, but collecting this information and following this up in the registers should be adequate measures to control for such confounding. Furthermore, results from the second patient dispensation analysis in study IV were not different from the first dispensation to suggest that patient uptake of β-blockers changed substantially over time.

Conclusions

The following conclusions can be drawn based from the papers in this thesis:

I. The 12-month post-MI follow-up of an iCBT intervention for MI patients with self-reported symptoms of anxiety or depression did not suggest an effect of treatment on symptom reduction or risk of CVD events, compared to the control group, but problems with low adherence is a limitation which makes conclusions difficult to be drawn. Improving adherence in digital interventions in similar trials is thus of great importance.

II. The involvement of the intended target group (PRPs) in designing a novel internet-based intervention was of great value for the work process. This was helpful and several modifications were made based on feedback from the group. This strategy is recommended as a collaborative effort for developing novel interventions, particularly in groups that are underrepresented or fall under a niche category.

III. The proposed iCBT-based intervention for patients with MINOCA or TS and planned procedures for using this intervention were found to be feasible in terms of study recruitment, data collection and internet delivery, thus indicating good support for success in the next phase of the RCT.

IV. Differential doses of β-blocker were not associated with HRQoL outcomes in first-time MI patients. RCTs such as the RQoL study comparing β-blocker treatment to no treatment, are needed to properly investigate the relationship between β-blocker treatment and HRQoL.

V. The early stages and reporting of the first 100 participants into the RQoL study show that the follow-up response rates, study functioning and digital data collection methods are acceptable.

Clinical Implications and future directions

Mental health research in the cardiac population, while somewhat well-researched, is none-the-less relatively new in comparison to its medical counterparts. Due to its interdisciplinary essence, many areas are often left open for possible future directions and investigation. This thesis covers studies that have collected and analysed data, as well studies in the early stages of planning; from design and creation, to feasibility testing and ongoing RCTs. This implies there is an opportunity to develop and learn from these future findings and results.

Future directions for e-health interventions in the cardiac population as a whole still have some way to go and develop further. As previously mentioned, a future direction for study II and III could involve the translation of

the intervention into other languages and provision of this by a psychologist/e-therapist who can provide feedback and guidance in that language. If results are positive for the effect of treatment on improving stress and anxiety, then offering this as part of the current healthcare offered to patients with MINOCA/TS should be considered following successful implementation evaluation.

Studies IV and V might also hold critical clinical implications for the future directions of the current care offered to MI patients as part of secondary prevention. β-blockers are still standard treatment, even in MI patients with LVEF ≥50%. Study V (and the ongoing RQoL RCT that it is based on) could shape the way future treatment is offered. This could be both in regards to the awareness of the prescribing of β-blockers in patients with normal LVEF and high psychological distress in general, and in the case of following up more closely MI patients whom report higher psychological distress, and are taking β-blockers, more closely. This research has the potential to affect a great deal of future decisions from both policy makers and healthcare professionals, to patients themselves.

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