e-Health treatment of stress and anxiety in Stockholm Myocardial Infarction with Non-obstructive Coronaries study

e-SMINC

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2. Background and rationale

Recent advances in diagnostics of acute coronary syndromes, such as high sensitive troponin assays and coronary angiography, have revealed a new entity of patients. Approximately six percent (5-15%) of all patients fulfilling the diagnostic criteria for myocardial infarction have no obvious cause in the coronary arteries i.e. < 50% stenosis (1). These events were recently labelled Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) that should be considered as a *working diagnosis*, which requires further investigation (2). Examples of diagnoses revealed during investigation of MINOCA are myocarditis, takotsubo syndrome and myocardial infarction due to plaque rupture or erosion. The most recent 4th definition of myocardial infarction have refined the *final diagnosis of myocardial infarction* to only include patients fulfilling the diagnostic criteria for myocardial infarction with a coronary cause, for example plaque disruption (3). Consequently, the troponin increase in myocarditis is described as myocardial injury and takotsubo syndrome is considered a separate entity. The management of MINOCA as a *working diagnosis* is not clear and there are no separate guidelines but one European position paper (2) and one American scientific statement (4). Recently, diagnosis and management of MINOCA was mentioned as a separate entity in the European Society of Cardiology guidelines for acute coronary syndromes in patients presenting without persisting ST-segment elevation (5). All emphasize the importance of further diagnostic investigations, in particular the use of Cardiac Magnetic Resonance (CMR) imaging and recommended treatment depending on the *final diagnosis*.

Patients with MINOCA often report anxiety due to the lack of a firm explanation for their illness and in many cases mental or physical stress are contributing parts to the syndrome. Patients with the working diagnosis MINOCA, including takotsubo syndrome, have a decreased health-related Quality-of-Life (QoL) compared to healthy subjects. Their QoL is similar and in some dimensions worse (mental stress and vitality) than patients with myocardial infarction due to Coronary Artery Disease (CAD)(6). Furthermore, anxiety and depressive symptoms are as prevalent in MINOCA as in myocardial infarction due to CAD (7). As described above, takotsubo syndrome is part of the *working diagnosis* of MINOCA but a separate *final diagnosis*. The above mentioned studies of the working diagnosis MINOCA (6,7) also describe sub-group analyses of patients with takotsubo syndrome showing exaggerated mental stress and anxiety when compared with MINOCA patients without takotsubo. Increased mental stress and anxiety in takotsubo patients have been confirmed in qualitative interview studies (8,9). One recent study of MINOCA (10) showed that patients, in particular women, rate their stress high on the Perceived Stress 14 Item Scale (PSS-14). Unpublished data from the Stockholm Myocardial Infarction with Normal Coronaries (SMINC)-2 study (11) showed that 60% of the patients with a *working diagnosis* of MINOCA report high levels of stress and/or anxiety, as determined by the questionnaires PSS-14 and HADS, during admission. At present there are no randomised studies of any treatment of MINOCA, including the *final diagnoses* of MINOCA and takotsubo syndrome. There is an urgent need for non-pharmacological alternatives aiming at relieving stress and anxiety considering the high mental stress and anxiety levels in MINOCA, including takotsubo syndrome, leading to decreased QoL. Cognitive Behavioural Therapy (CBT) aiming at reducing mental stress has been shown to be effective regarding prognosis in patients with CAD (12). The current protocol describes a randomized controlled trial evaluating an internet-based CBT program for reduction of stress and anxiety in patients with increased mental stress and/or anxiety and a *final diagnosis* of either MINOCA or takotsubo syndrome.

3. Objectives and design

The overall aim is to study the effects of an internet-based CBT intervention on perceived stress and anxiety in patients with MINOCA and takotsubo syndrome compared to controls

receiving usual care**.** A secondary aim is to compare immediate CBT intervention (start within 2-4 weeks) with late intervention (start within 12-14 weeks).

4. Study setting

Academic hospitals in Stockholm and other selected sites with an interest in MINOCA, Sweden

5. Inclusion criteria

Inclusion criteria are:

- a suspected diagnosis of MINOCA or takotsubo syndrome with coronary angiography without diameter stenosis ≥50%
- age ≥ 35 years
- PSS-14 ≥ 25 and/or HADS-A ≥ 8 during admission
- reading and writing proficiency in Swedish
- computer/Internet access and literacy

6. Exclusion criteria

Exclusion criteria are:

- strong clinical suspicion of myocarditis
- spontaneous coronary artery dissection
- acute pulmonary embolism
- acute myocardial infarction type 2
- cardiomyopathy other than takotsubo syndrome
- a previous myocardial infarction due to CAD
- expected poor compliance to behavioural therapy
- not likely to survive > one year due to for example cancer

7. Intervention

The intervention is a nine-step psychologist-guided internet-delivered self-help program, based on CBT. It will be delivered via a secure on-line platform, the portal, using secure authentication for log in. All nine intervention steps include short informative texts and examples, as well as assignments that the participant report in the portal. The self-help material also include both audio and video files. Participants will be encouraged to complete one step in the self-help program each week.

The first step includes written medical information about MINOCA and filmed interviews with patient and health-care personnel. Diagnosis and recommended treatments are covered and common reactions after a cardiac event are presented. Participants are asked to describe their cardiac event and how it has influenced their lives.

The following four steps, focus on stress. Step 2 is mainly psycho-educative, and introduces self-monitoring of stressors and stress reactions. In Step 3 specific and personal stress situations are identified, including a discussion on short- and long-term consequences of stress behaviors. Step 4 focuses on recovery and relaxation. In Step 5 central personal values are identified and behaviors in line with these values are encouraged.

In Step 6, the concept of heart-related fear, worry or anxiety is introduced. Participants recognizing these kinds of worries are encouraged to work through steps 7-8, including psycho-education relating to fear, worry and anxiety, self-monitoring of difficult situations and avoidance behaviors, formulation of an exposure hierarchy, and heart-related exposure training. Participants that do not experience heart-related fear, worry or anxiety can go directly to Step 9.

In the last step of the program, Step 9, the participants will be working on a summary of what they have learned during the intervention, and how these advances can be maintained or further developed.

On completion of the first intervention step, the psychologist will contact each participant by phone to establish report and discuss treatment goals. Throughout the rest of the program, participants will receive personalized written assignment feedback from their psychologist. The participants will also be able to contact their psychologist using a text message function within the portal.

8. Outcomes

8:1 Primary outcome

Self-rated stress and/or anxiety, as a categorical measure, 12-14 weeks after the index event

8:2 Secondary outcomes

Self-rated stress, anxiety, QoL, cardiac anxiety and post-traumatic symptoms, as continuous measures, 10, 20 and 50 weeks after randomisation

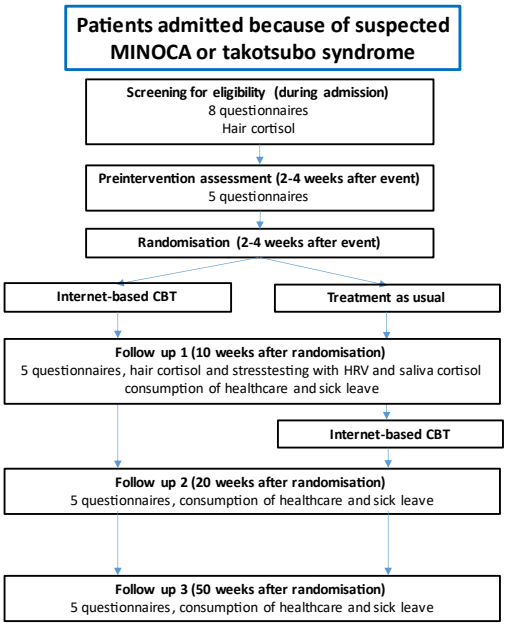
Biological stress 10 weeks after randomisation

Physiological recovery after stress 10 weeks after randomisation

Self-reported total number of sick-leave days 10, 20 and 50 weeks after randomisation

Self-reported total number of health-care visits 10, 20 and 50 weeks after randomisation

9. Flow chart of study time-line



10. Sample size

By including 90 patients (45+45 patients) we will be able to detect a 30% absolute difference in the number of patients per group that have normalized the scores on PSS-14 and/or HADS-A (80% power, $p < 0.05$) taking into account that 45% of patients receiving usual care had

normalized their PSS-14 and/or HADS-A at 6 months (unpublished results). 90 patients compensate for a loss of 10 patients missing follow-up measurements.

11. Methods

The secure web-platform, the portal described above, will be used to collect information about background factors such as patient characteristics and history as well as for the questionnaires and information about health-care contacts and sick-leave. Thus, the majority of information is self-reported rather than investigator-reported with the exception of the biological stress measures.

11:1 Assignment of treatment

All patients will be introduced to the study by the study site. Randomisation will be made by computer-generated random numbers in blocks of 6 within the internet-portal described above. The treatment will be guided by psychologists involved in the trial within the portal.

11:2 Questionnaires

Self-related stress will be determined by **Perceived Stress Scale (PSS-14)** which is a self-reported questionnaire measuring levels of stress and coping (13). PSS-14 contains 14 items that are rated on a 5-point Likert scale, from 0 (never) to 4 (very often) with a total score between 0 and 56. High scores indicate more perceived stress. The threshold for increased levels of stress is 25. PSS 14 has two subscales where seven of the items measures stress, while the other seven items measures coping ability. The Swedish version of PSS-14 has been shown to be reliable and valid in patients with or without known stress-related conditions (14).

Self-rated anxiety will be determined by **Hospital and Anxiety Depression Scale (HADS)** which is an instrument for assessment of symptoms of anxiety and depression (15). It has two subscales, one for anxiety (HADS-A), and one for depression (HADS-D), each consisting of seven items that are rated on a 4-point Likert scale (0-3) with a total score between 0 and 21. A cut-off point of 8 can be used to identify potential cases of anxiety and depression. HADS has been validated in a Swedish population and shown to have a reliable factor structure (16) and been frequently used in several studies on different CAD groups in Sweden and elsewhere.

Self-rated cardiac anxiety will be determined by **Cardiac Anxiety Questionnaire (CAQ)** which is an instrument used to measure heart-related anxiety developed for patients with chest pain (17). It consists of three domains: fear of cardiovascular sensations, avoidance of activities that may trigger them and heart-focused attention. The scale comprises 18 statements rated on a Likert type scale ranging from 0 (never) to 4 (always) with a total score between 0 and 72. CAQ has demonstrated good reliability and validity and been used in several Swedish patient groups including patients with chest pain with or without CAD and is associated with psychological distress (18).

Self-related QoL will be determined by **Rand-36** that is a free version of the generic QoL questionnaire Short Form-36. It contains 36 items in eight domains of QoL and gives a range between 0-100 where a higher value indicates better QoL. The Swedish version of Rand-36 has been validated in cardiac patients (19).

Self-rated post-traumatic symptoms will be determined by **Impact of Event Scale 6 item version (IES-6)** which is a short form version of the Impact of Event Scale Revised version (IES-R)(19). It is a brief measure capturing symptoms of post-traumatic stress relating to a specified event. The IES-6 includes two IES-R intrusion items, two avoidance items, and two hyperarousal items all rated on a Likert type scale ranging from 0 (not at all) to 5 (very much) with a total score between 0 and 30. The IES-6 accounted for 91% of the variance in the full IES-R and possessed screening properties similar to the IES-R when compared to the posttraumatic stress disorder checklist (20). The Swedish version of IES-R has been shown to have good properties as a screening tool for PTSD (21).

<u>The following questionnaires will be used at admission to investigate possible predictors of mental stress and anxiety:</u>

Intolerance of Uncertainty Scale (IUS 12) is a brief self-report tool for evaluating general intolerance of uncertainty (22). The 12 items are rated on a Likert type scale ranging from 1 (not at all characteristic of me) to 5 (entirely characteristic of me). The total score (12-60) indicates general intolerance of uncertainty with higher scores reflecting greater reports of intolerance. The scale can also be divided into two factors: Prospective anxiety (fear and anxiety based on future events) comprising 7 items and inhibitory anxiety (uncertainty inhibiting action or experience) comprising 5 items. The English version of the IUS 12 has

shown strong internal consistency and high correlations with the original IUS and related measures of anxiety and worry (23), while the Swedish translation is yet to be validated.

Difficulties in Emotion Regulation Scale (DERS 16) is a brief assessment of overall emotion regulation difficulties (24). It consists of 16 items that assess six dimensions of emotion regulation difficulties: non-acceptance of negative emotions, inability to engage in goal-directed behaviors when distressed, difficulties controlling impulsive behaviors when distressed, limited access to emotion regulation strategies perceived as effective, and lack of emotional clarity. Respondents are asked to rate the extent to which each item applies to them on a 5-point Likert-type scale from 1 (almost never) to 5 (almost always), giving the DERS-16 a range of 16 to 80, with higher scores reflecting greater levels of emotion dysregulation. The Swedish version of DERS 16 has shown very good psychometric properties, with excellent internal consistency, good test-retest reliability, and good convergent and discriminant validity (24).

Global/general attachment subscale of the Experiences in Close Relationship-Relationships Structure (ECR-RS) questionnaire is an instrument for brief evaluation of an individual's global adult attachment (25). In nine items, participants are asked to rate how they generally think and feel in close relationships. Each item is rated on a 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree). The first six items tap attachment-related avoidance (i.e. how comfortable the individual is with closeness and dependency) and the three remaining items capture attachment-related anxiety (i.e. the extent to which an individual is concerned about being rejected by others). High scores on either of the two subscales reflects higher levels of attachment-related avoidance and/or anxiety. The Swedish version of ECR-RS has shown good internal consistency, as well as good convergent and discriminant validity, and multi-group invariance tests for gender and age showed no violations to invariance (26).

11:3 Stress test

There are many different mental stress provocations used to test the balance between vagal and sympathetic activity. The mental stress test presented below has been used previously in patients with takotsubo syndrome (27). The first part, known to increase sympathetic activity,

consists of two tasks, presented in one block, starting by an anger recall interview where the patient is asked to recall an upsetting situation during the last few months prior to the investigation and then speak about that situation for a 2-3 minutes. Follow-up questions about this upsetting situation are asked by the interviewer. The anger recall interview is immediately followed by a mental arithmetic task in which the patient is asked to subtract 7 from a 4 digit number in consecutive steps as fast as possible. This part of the test is performed under increased stress induced by the test-leader by asking the patient to count faster. The second part of the mental stress test consists of a recovery phase potentiated by an imagery task (comprising a secure place or person) shown to increase vagal activity (28). Recovery time is defined as the time it takes for the patient to reach baseline levels of heart rate and blood pressure.

11:4 Biological stress measures

Cortisol is a method to measure biological stress (29). Traditionally, cortisol measurements made in blood, saliva or urine gives an estimate of the most recent stress including both mental and physical stress, hence s*aliva cortisol* will be used to measure acute stress before and after the planned stress test. Long-term stress can be measured by frequent samples of saliva cortisol, including 2-5 samples/day, repeated several days during the whole time-period of interest or by hair cortisol. One centimeter of hair taken from the scalp reflect one month of cortisol exposure. *Hair cortisol* will be measured at randomization and after the intervention. Hair and saliva cortisol will be measured by RIA-technique.

Heart-Rate-Variability (HRV) is a method to measure autonomic activity (30). HRV is caused by the balance between vagal and sympathetic nerve activity, reflected in alterations in heart rate, i.e. heart-beat intervals. In general, increased HRV reflect a relative increase in vagal to sympathetic nerve activity and is associated to low mental stress. HRV can be assessed by time-domain, frequency domain and non-linear methods. HRV will be determined after the intervention before and after the mental stress test from a 10 minutes ECG-recording, both in the time-domain (SD, SDNN and others), frequency domain (HF, LF and VLF), and by nonlinear methods (such as Poincaré plots). The ECG will be recorded as a single-lead ECG with very high resolution (10 000 Hz; PowerLab, ADInstruments) using a specific electrode positioning that also enable us to measure skin sympathetic nerve activity as a surrogate of cardiac sympathetic nerve activity, as previously described (31).

11:5 Data collection and management

All data, with the exception for the biological stress measures, will be collected by the secure platform, the portal, hosted by Uppsala University. All personal data will be handled according to GDPR.

11:6 Statistical methods

Continuous data will be presented as median with interquartile range or by mean and standard deviation, and categorical data as numbers and percentages. Comparison of continuous data will be made by linear regression or mixed models with post-measures as outcome and, group allocation and pre-measures as covariates. Calculations of effect size will be performed by Cohens *d*. Categorical data will be analyzed by Chi2-test. The outcomes will primarily be analyzed as intention-to-treat. As a post-hoc analysis, patients who completed ≥5 steps of the intervention will be compared with treatment as usual. The outcomes will be analyzed by Chi2-test of normalization of PSS-14 and/or HADS-A (categorical data) and by linear regression or mixed models (continuous outcomes) using the measurements made at randomisation (2-4 weeks) as pre-measures. Clinical significance will be determined according to the method by Jacobson and Truax (32).

12. Monitoring

There will be no data monitoring since data are self-reported and the patients with active treatment will be followed continuously by psychologists involved in the trial. There will be an audit of the recruitment process by independent monitors from Södersjukhuset at the end of the trial.

13. Ethics

The study has applied and received permission (December 17, 2018) to perform the trial from the Regional Ethics Committee in Stockholm (2018/1434-31/1).

The permission includes oral and written informed consent from all included patients. All personal data will be saved securely by Uppsala University according to GDPR. Only the members of the steering committee and doctoral students will have full access to the data.

The results of the study will be presented at national and international conferences and published in an open access peer-reviewed journal including authorship by all members of the steering committee and selected doctoral students.

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