

RESEARCH PROTOCOL

Tilburg Health Outcomes Registry of Emotional Stress in Coronary Intervention (THORESCI)

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Protocol ID	NL46259.028.13
Short title	THORESCI
EudraCT number	N/A
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
IC	Informed Consent
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
PCI	Percutaneous Coronary Intervention
PI	Principal investigator
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale: Percutaneous coronary interventions (PCI) have become mainstay treatment for acute coronary artery disease and the number of patients receiving PCI is vastly growing. Clinical trials have reported on the efficacy and effects on quality of life and mortality. Guidelines have been constructed for PCI treatment as well as cardiovascular prevention. However, relatively little long-term follow-up studies of large real-world clinical samples exist that have looked at the real-world effects of PCI treatment and adherence to current guidelines.

Moreover, psychological risk factors are important in determining prognosis after PCI, and undergoing PCI may increase the risk of low mood. To date, studies have examined single psychological risk factors, without taking into account their relatedness. Moreover, guidelines are advocating psychosocial screening in early cardiovascular disease, but the screening test as proposed in the ESC Prevention guideline has not yet been validated or tested. **Importantly, recent studies have indicated the need to examine**

Although the detrimental effects of psychological risk factors on cardiovascular prognosis are known, the mechanisms through which they exert these effects are yet unclear. It is to be expected that not one but multiple biological (inflammation, endothelial dysfunction) and behavioural (coping styles, poor self-care, consultation behaviour, decision making process) pathological processes play a role, and that these processes interact with each other. In PCI patients, the mechanisms linking psychological risk to poor prognosis are still to be investigated. **Objective:** (1) To examine the adherence to the prevention and PCI guidelines and the effects thereof on long term prognosis in PCI patients. (2) To examine effects of clustering psychological risk factors on several networks of potentially mediating mechanisms and long term outcomes in a large sample of PCI patients. (3) To evaluate the effectiveness of the adapted psychosocial screening instrument of the European Society of Cardiology Prevention guideline 2016. **Amendment objective:** in this additional analysis and secondary data collection made possible by ZonMw, we aim to investigate gender differences in screening scores as well as gender differences in the association between screening and psychological and medical outcome. **Additionally, due to the extraordinary circumstances of the COVID-19 pandemic, we would like to ask participants about how this affected their cardiological care.** **Study design:** Prospective observational cohort study. **Study population:** All patients aged >18 admitted to the TweeSteden hospital for percutaneous coronary intervention are eligible. **Main study parameters/endpoints:** *Predictors:* Psychological (risk) factors (depression, anxiety, Type D personality, mindfulness, positive mood), Adherence; *Outcome variables:* PCI complications, hospitalizations, events. **Additional variables:** gender assessment **Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** The risk associated with the current study is very low. For this mechanistic observational study, investigators will ask patients to fill out two extensive (20 pages) and then several smaller (12-15 pages) psychological surveys including among others questions on personality, positive and negative mood, mindfulness, work stress, and satisfaction with life. Preferably, questionnaires will be administered digitally by email link. **For the additional data collection (gender + covid), an additional questionnaire is added that will be sent once to all participants in the fall of 2020. It will take 15 minutes to fill out this additional questionnaire.** There are no direct benefits of participation, other than providing data to create knowledge to improve future treatment.

1. INTRODUCTION AND RATIONALE

Cardiovascular disease (CVD) is a global disease burden and a leading cause of death and disability, with about 23.6 million people expected to die from CVD worldwide by 2030¹. Percutaneous coronary intervention (PCI) is a state-of-the-art non-surgical procedure to treat stenotic occlusions of the coronary arteries in patients with cardiovascular disease by inserting a balloon and stent into the diseased artery to treat the occlusion. Randomized controlled trials have shown the efficacy of this procedure for prognosis of cardiac patients^{2,3}, and this evidence is supplemented by effectiveness studies in real-world clinical samples that show differential prognoses after PCI in important subgroups, such as women, and patients with diabetes, poor cardiac pump function, or multivessel disease^{4,5}. Also quality of life improves after PCI, both in younger and older cardiac patients⁶.

Besides traditional medical and demographic risk factors for poor prognosis of CVD, psychological factors also have been associated with poor prognosis in CVD⁷. In PCI patients specifically, psychological factors, such as depression^{8,9}, lack of positive emotions¹⁰, and feeling disabled a few months after the PCI¹¹, have shown to have a detrimental impact on mortality. Screening for these factors does not happen structurally, and if a screening is done, it usually comprises depression and anxiety only, while a range psychological risk factors have been identified.⁴⁷ To do right to this myriad of psychosocial risk factors, we want to examine the effectivity of a psychosocial screening interview that is workable in clinical practice (i.e. short), and that covers the full range of established risk factors.

1.1 Investigating long term effects and interrelations between psychological risk factors

Longer term effects of PCI procedures with respect to efficacy and effectiveness until now have been examined over periods of on average about 3 to 4 years of follow-up², and focus primarily on complications, MI and early death, although some studies with longer follow-up periods exist comparing differences in prognosis for different stent types e.g.,¹². With respect to psychological risk factors, the long-term (7-year) predictive value of depression on all-cause mortality has been shown^{8,10}. However, psychological factors in these two studies have only been assessed at baseline (between 0-6 months post-PCI), while it is important to look at depression profiles (which symptoms dominate) and persistence of depressive symptoms over time. It has been shown that somatic symptoms of depression predict mortality better than cognitive symptoms in stable coronary artery disease patient¹³⁻¹⁵. Also, both in heart disease patients¹⁶ as well as in the general population¹⁷ these symptom profiles have been differentially related to inflammatory activity, a proposed mechanism in the relation between depression and cardiovascular prognosis. In patients with acute coronary syndrome associations have also been reported on somatic a cognitive depression scores at baseline, and inflammatory activity, i.e. hsCRP levels, at 1 and 3 months follow-up, suggesting that depression might affect prognosis^{18,19}.

Besides the demonstrated relevance of discriminating between different psychological symptom profiles, it may also be important to discriminate between cardiac related and all-cause mortality and events, as previous studies have shown that only looking at all-cause mortality may delude the effect you are after. Surely, the mechanisms underlying cardiac mortality may not be equal to other pathophysiological processes leading to other causes of death.

It is thus necessary to increase the level of detail in the relation between psychological risk and prognosis to be better able to pinpoint which patients are in need of additional care. To start finding

out more about the course and progression of heart disease in patients with psychological risk factors, large registries of heart disease patients that are in the early stages of heart disease are needed, and long follow up periods in such registries is warranted. To date, there is no registry that systematically screens for psychosocial risk factors, as well as systematically and regularly assesses psychological risk factors over longer time periods in patients undergoing a percutaneous coronary intervention. Such a registry is necessary to evaluate the role of psychosocial factors in the effectiveness of PCI. Therefore, the current study aims to extend the current standard of care registry of PCI patients to include a yearly inventory of events (revascularisation, MI) and mortality for at least 10 years. In addition, we aim to add a long term psychological survey study. These data will enable us to answer the following research questions:

- What are the long term clinical, psychological and demographical predictors of cardiovascular events and mortality in patients that have received a PCI procedure?
- How do psychological risk factors cluster together in increasing the risk of events/mortality?
- How do psychological risk factors behave over long periods of time in an at-risk cardiovascular population? Can we identify symptom profiles over time that are useful in risk stratification?
- What behavioural mechanisms play a role in explaining the association between the found risk factors and events/mortality?
- What are the long term clinical, psychological and demographical predictors of quality of life in patients that have received a PCI procedure?
- How does quality of life change over time?

1.2 Exploring mechanisms of effect

Allostatic load is increasingly used as a general indicator of cumulative burden of physiological dysregulation. Allostatic load is usually defined as a count-based index of multiple biomarkers including markers of neurohormonal activity, lipid and glucose metabolism, cardiovascular and immune system activity, and indices of visceral obesity ²⁰. The proposed projects will focus on allostatic load as a hypothesized pathway through which emotional distress exerts its detrimental effects on cardiovascular health, but will take a different operational approach. To date, most previous mechanistic risk assessment studies have either published on the risk of individual markers or have not taken into account their interrelationships and interactions e.g., ^{21,22-25}. Others have used summary scores of allostatic load that do not take into account higher-order constellations of dysregulations across multiple major regulatory systems ²⁰. A recent novelty is to use structural equation modeling to examine the cardiovascular health risk of multiple individual biomarkers in the context of the system of interrelations ²⁶.

Importantly, psychological, behavioral and biomedical risk factors interact with, and may be influenced by, the major regulatory biological systems in the human body that adapt in response to stress. The current project will therefore take into account the interactions between the allostatic load components and the behavioral risk factors. By taking such a broad multisystem approach, this proposal will arrive at a more informative and complete cardiovascular risk assessment.

Research questions that will be answered are:

- Which variables of the network of biological regulatory systems are most important in determining prognosis in PCI patients?
- In what way are psychological risk factors related to the network of biological regulatory systems? Are there differences between psychological risk factors?
- To what extent do behavioral factors moderate the relation between psychological risk factors and prognosis?

1.3 Extending the PCI registry to include participation in cardiac rehabilitation

Cardiac rehabilitation (CR) is a multifaceted intervention program that aims to improve physical, psychological and social functioning of cardiac patients after a cardiac event or therapeutic intervention, such as PCI ²⁷. In addition to these primary objectives, CR also aims to induce lifestyle changes and improve medication adherence ²⁷. It has been shown in previous studies that actively attending cardiac rehabilitation (CR) has beneficiary effects on survival after percutaneous coronary intervention. A recent study in 2395 consecutive patients showed that a reduction of risk of (HR=0.55) for all-cause mortality after a median follow-up of 6.3 years in those patients that had attended CR ²⁸. Recent PCI guidelines recommend cardiac rehabilitation for all patients recovering from PCI ²⁹. Unfortunately, only a limited part of eligible patients (between 13-40%) actually participate in CR ^{28,30}. In the Netherlands, the same picture may be painted, with less than 1 out of 3 eligible patients participating ³¹. Recent insurance data from the Netherlands has even indicated that only a very small minority (11%) of patients with an elective PCI attends CR ³². At the TweeSteden hospital, all PCI patients are invited to participate in CR, but as yet, there is no record of who participates and who does not. Therefore, the current research proposal aims to extend the current medical outcome registry of PCI patients to include data on recruitment for and participation in cardiac rehabilitation. Also, data will be gathered on which combination of treatments are offered to the patient.

Patients get more and more involved in their own treatment and treatment decisions. There seem to be large differences between specialisms though in the extent to which patients participate in the decisions of their own treatment. This is a very timely issue and here has been only one previous study examining the extent of shared decision making in patients recovering from an ischemic coronary event ⁴⁶. Their results show that shared decision making did not happen as often as patients would want, and there were significant sex differences as well, with women being less informed and less involved. This is a Canadian study, so we are in need of a European study looking into this aspect of care.

These data will enable us to answer the following research questions:

- What is the participation rate and adherence to cardiac rehabilitation?
- Which clinical, psychological and demographic variables are predictors of adherence to cardiac rehabilitation in patients that have received a PCI procedure?
- Which phases in the patient recruitment for cardiac rehabilitation may need improvement? What is the role of physician adherence and what are predictors of non-participation?
- To what extent was there a shared decision making process in the decision whether or not to start cardiac rehabilitation?

1.4 The role of sex and gender

In clinical research and practice, it is of importance to consider diversity and heterogeneity. Women experience more psychosocial complaints such as anxiety and depression^{33,34}. A recent meta-analysis of data on over 220.000 women and 320.000 men has shown that depression and anxiety in men incur larger risks of poor prognosis in patients with ischemic heart disease compared to women³⁴. Differences in etiology and prognosis between men and women are, at the moment, not included in treatment.

In addition, there are sex and gender differences in other psychological risk factors. For example, early life events are more prevalent in women, and the effects of these early life events on the incidence of heart disease is larger in women too³⁵. In the THORESCI study, the clustering of risk factors has already been examined³⁶. Results showed that the profile characterized by anxious tension was more dominant in female patients, while hostility, anger and generalized distress were more common in male patients. We do not know whether gender will show us more diversity in risk profiles. More masculine identifying women may have a different risk profile as compared to more feminine women and for men similar discrepancies may exist. That is why the current additional project funded by ZonMW will focus on the role of sex and gender in psychosocial risk profiles and their association with outcomes.

1.5 Scientific and societal relevance

Cardiovascular disease comprises a considerable burden to society and patients due to increased health care costs and limitations to quality of life. About 25-50% of patients with cardiovascular disease have psychological problems as well, and these individuals also more often have precursors of cardiovascular disease (i.e. metabolic syndrome, hypertension) and have a worse prognosis and quality of life than patients without psychological risk factors. The current research proposal aims to increase the knowledge of explanatory mechanisms in this relation between psychological risk and poor outcome. This may open up new avenues for preventive and curative treatment tailored to the specific biological and behavioural underpinnings of individuals with psychological risk factors. Over time, these psychologically directed preventive and curative treatments may be able to reduce health care costs and thereby the burden to society.

Part of the results of the proposed projects embedded within the proposal can be implemented in clinical practice on the short to midterm. After the psychosocial screening has been validated in the current study, psychosocial screening can be adopted quickly and at low cost and can help in earlier risk stratification. In addition, when the results of the current project would show that health behaviours are important moderators of the relation between psychological risk and cardiovascular disease progression, behavioural programs that focus on losing weight, quitting smoking, as well as exercise programs are readily available during CR, but could be tailored to for example Type D individuals, taking into account their fear of social engagement.

On the longer term, uncovering biological mechanisms that are important in determining the cardiovascular risk of patients with psychological risk factors, could guide the development of

treatment strategies that target these biological mechanisms. For example, inflammation can be suppressed with anti-inflammatory drugs and it should then be investigated whether these anti-inflammatory drugs may also reduce the risk of poor prognosis of cardiovascular disease in patients with psychological risk factors. Also, it is possible to train autonomic regulation of the heart using biofeedback. Increasing parasympathetic and decreasing sympathetic cardiac drive using biofeedback might be another treatment avenue.

A further valorization aim of the current proposal is to inform and to educate. The first aim is to inform the public, especially patients with cardiac disease and people at risk for cardiovascular disease. As soon as the results of the projects are known, the researchers will contact the patient organization “De Hart & Vaatgroep”, to invite them to a symposium about the results of the research project. There have been previous contacts between our research institute CoRPS and this patient organization, so future contact will not be hampered by unfamiliarity. Also, outpatients of the cardiology clinic that participate in the study will receive a yearly newsletter informing them about the research project and the results. The overarching aim being that educating patients about the impact of psychological factors and health behaviours on disease progression and quality of life, and the mechanisms behind these effects, might improve adherence to treatment as well as consultation behaviour.

The second aim is to educate medical specialists on the role of psychological factors in disease prognosis and the mechanisms involved. Together with the Brabant Medical School the applicant will organize a seminar during which the results of the study are reported to medical residents and specialists. The PI has experience in collaborating with the Brabant Medical School, as she initiated the development of a statistics course for medical residents for the School.

2. OBJECTIVES

2.1 Primary Objectives

1. To establish a real-world standard for understanding disease progression and outcomes in cardiac patients who receive a percutaneous coronary intervention
2. To examine the effectivity and usefulness of psychosocial screening in cardiac patients who receive a percutaneous coronary intervention
3. To examine biological and behavioural mechanisms potentially explaining the link between psychosocial risk and cardiac prognosis.

2.1.1 Hypotheses

1. The real-life standard will deviate from samples from clinical trials in descriptive statistics as well as in outcomes and outcome prediction.
2. Psychosocial screening will serve a general signalling function to identify at-risk patients. These at-risk patients will be characterized by poorer adherence to treatment guidelines, increased report of symptoms and complications, as well as with a lower participation rate in cardiac rehabilitation.
3. Patients with psychological risk factors such as depression, anxiety and Type D personality will be characterized by increased chronic low grade inflammation, more endothelial dysfunction and higher levels of myocardial damage markers.

2.2 Secondary Objectives

1. To study socioeconomic and gender differences in prognosis after a PCI procedure and their interaction with psychosocial risk
2. To examine long term course of psychosocial risk factors in cardiac patients after a PCI procedure.

2.3 Amendment objectives

1. to examine the relation of sex and gender with the various psychosocial risk profiles.
2. To examine sex and gender differences in health behaviors, classical cardiovascular risk factors and medical history, that are known to differentially relate to the various psychosocial risk profiles.
3. to examine the moderating role of sex and gender on the relationship between psychosocial risk profiles and health outcomes.
4. With respect to Covid-19, the current study would like to examine to what extent the THORESCI patient population has experienced a delay in care, and to what extent Covid-19 is related to a larger proportion of adverse events in the pandemic aftermath.

3. STUDY DESIGN

This is an observational cohort study, which recruits participants from the clinical standard of care PCI Registry at the TweeSteden Hospital. Yearly, approximately 800 patients receive a percutaneous coronary intervention at the TweeSteden hospital. Of these, about 400 undergo an elective or sub-acute procedure, and these patients will be asked to participate in this research project until the Trigger study (a CoRPS PhD project) has ended their data collection in acute PCI patients (estimated to end in 2015 at the latest). After that time, also acute PCI patients will be included. Please see below flow chart for an overview of the study design.

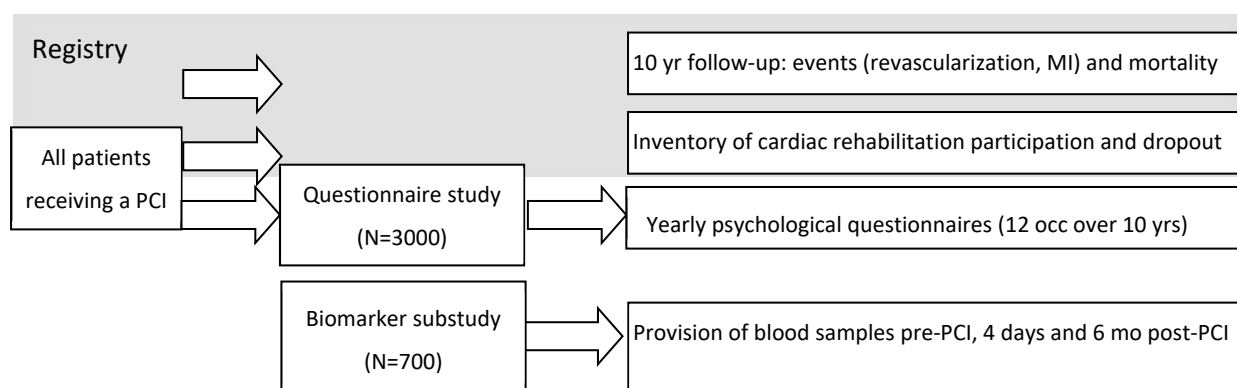


Figure 1. Main PCI registry Study design

4. STUDY POPULATION

4.1 Population (base)

- *Registry*

All patients (all ages, male and female) from the Cardiology clinic of the TweeSteden hospital who are going to be scheduled for elective or acute percutaneous coronary intervention for ≥ 1 coronary occlusions are to be included in the PCI standard of care registry. About 800 patients/year receive this procedure, which amounts to an average of 15 PCIs per week. The standard of care registry in the TweeSteden hospital is obligatory, because the TweeSteden hospital is a relatively new PCI centre. The registry includes both acute and elective PCI patients.

- *Questionnaire study*

The questionnaire study will first include patients with an elective or subacute PCI procedure (until end 2015), who participate in above described registry, as in acute patients there is no time for pre-procedure screening. After that time, we will also include acute PCI patients, and aim to include in total 3000 participants in the questionnaire study over a period of 5-6 years, expecting a participation rate of 75%.

4.2 Inclusion criteria

In order to be eligible to participate in the *Questionnaire study* and the *Biomarker substudy*, a subject must meet all of the following criteria:

- Aged ≥ 18
- Sufficient understanding of the Dutch language to fill out questionnaires

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in the *Questionnaire study*:

- Life threatening comorbidity (e.g. metastasized cancer)

4.4 Sample size calculation

The essence of a registry is that the general aim is to include all patients in order to get the most complete picture of the real-world clinical situation and the real-world effects of treatments and risk factors. Therefore, sample size for the registry is unlimited. To be able to make conclusions on the effects of mortality, large samples and long term follow-up periods are needed as well. In the RESEARCH registry in Rotterdam, which also is a PCI registry, the 7-year all-cause mortality rate was 15%. Only 7% of PCI patients die from cardiac causes. Analyses in PASS executed by a CoRPS statistician (dr. Zijlstra), using information from previous studies (RESEARCH registry Rotterdam), have pointed out that with an expected 7-year event rate of about 8% (cardiac death), an estimated hazard ratio of 1.5 (dichotomous predictor), taking into account a predictor prevalence of 25%, with an accompanying an SD of 0.45 (depression data has been used for this power analysis), the minimal sample size needed for this study to be sufficiently powered is 2842³⁷.

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

Questionnaire study

Endpoints

- Mortality (all-cause and cardiovascular)
- Hospitalisations during the first year post-PCI
- Major adverse cardiac events (revascularization, MI, CABG, heart transplantation)
- Health complaints (self-report)
- Quality of life, satisfaction with life (self-report)

Psychosocial screener

Right after the PCI, in the clinic, and after consent, all participants will take part in a 5-minute screening interview which was adapted from the screening interview published by the European Society for Cardiology in their Cardiovascular Prevention guideline of 2016 (Piepoli et al., see appendix 1). During the past 6 months, I (PI) have been working together with an international group of researchers involved with the Cardiovascular prevention Guideline of European Society of Cardiology to make improvements to the original screener, which we have finalized recently. If participants indicate they are not up for an interview or the medical status precludes an interview, we will call the participant at 4 weeks follow up.

Questionnaires

Demographic variables (Baseline and at 1 and 2 years follow-up)

Date of birth, sex, educational level, work status, marital status, socioeconomic status, income level (8 items)

Anthropometrics (All measurement occasions)

Waist and hip circumference, weight, length (*Baseline only*), birth weight (*Baseline only*), gestational period (*Baseline only*) (6 items)

Lifestyle variables (all measurement occasions)

Smoking, alcohol use, diet, exercise

Personality (Baseline and at 1 and 2 years follow-up)

Neuroticism (*EPQ-NE*), extraversion (*EPQ-NE*), Type D (*DS-14*), mindfulness (*FFMQ*), optimism (*LOT-R*), cardiac self-efficacy (*CSAQ*), resilience (*RS-NL*), hostility (*MC 7-item Williams subscale*)
Spielberger trait Anger Questionnaire (*STAQ* 10 items), self-rating inventory for PTSD (*SRIP* 22 items) at 1 and 6 month follow-up

Mood (all measurement occasions)

Depression (*PHQ-9*, *BDI-II*), general anxiety (*GAD-7*), positive mood (*GMS12*), Worry (*PSWQ*)

Emotion regulation (Baseline, 30 days, and at 1 and 2 years follow-up)
 coping style (*CISS*), psychological mindedness (*BIPM*)

Shared decision making: 9 item *SDM-Q-9* at T1 and T2

Chronic stress (Baseline and at 1 and 2 years follow-up)

Life events (*Levensgebeurtenissen Vragenlijst*), effort-reward imbalance (*ERI*), marital quality (*MMQ-6*)

Additional Questionnaire

Gender - Bem sex roles inventory (12 items) + some demographic role division questions (breadwinner, household work, care and relationship tasks). The Bem sex roles inventory³⁸ measures feminine and masculine gender roles.

Covid-19: 13 questions on the alterations in medical care in the past half year (delay, video calls, etc), whether patients were infected and /or hospitalized for Covid-19. And, if so, how did it affect their heart condition until now.

5.1.2 Other study parameters/endpoints

Clinical variables (see appendix II)

5.2 Study procedures

Inclusion procedure Questionnaire study:

When after catheterisation the decision is made that the patient is a candidate for PCI, the *heart team* discusses its case, and a letter and information brochure is sent. In this mailing the patient will be informed about the registry as well as the questionnaire and biomarker study. After the PCI procedure, a research assistant will explain the questionnaire study to the patient and will give the patient information letter, informed consent, refusal form, first questionnaire and return envelope. They are asked to decide whether they are willing to participate in the study, and if so, whether they want to fill out the questionnaire and return it together with the signed informed consent within the next week. If not, they are asked to return the refusal form. If after 2 weeks nothing has been received, a phone call is made to the patient to ask whether the patient has decided whether or not to participate. .

Screening

The screening interview will take place immediately after consenting in patients that had undergone an elective procedure and acute PCI patients who are up for it and well enough to answer questions. The remained of the acute patients, or if patients indicated they are not up to it, will be called at 4 weeks follow-up to do screening interview. The screening interview takes five minutes to complete.

Questionnaire data collection procedure:

Patients will receive multiple questionnaires, at right after PCI, 30 days post-PCI, 1 year post-PCI and then yearly for the following 10 years. Because of the high number of potential participants we are aiming at, a link will be sent to participants to a digital, web-based questionnaire. When participants explicitly ask for a paper version, we will comply with this request. When a questionnaire is not returned (through the web-based program) within 2 weeks after the measurement occasion, a reminder email is sent. Medical data of the patients participating in the questionnaire study will be obtained from the registry and the patient's electronic medical record.

Blood collection procedure:

To be able to obtain the pre-PCI blood sample from the arterial sheath (right before catheter insertion), in all acute PCI patients this blood should be collected. After PCI, when still at the Cardiology inpatient ward, patients will be asked to participate in the study. When patients refuse, the blood collected pre-PCI will be instructed to be destroyed. This is a common procedure, that also takes place for multiple studies in PCI patients in the Erasmus MC in Rotterdam. For the biomarker substudy, participants are asked to provide in total 3 blood samples, pre-PCI, after 30 days, and after 12 months post-PCI. When patients do not want to participate in the study, or blood sub study, the pre-PCI sample is destroyed. The 12 month sample coincides with a regular clinic visits during which blood is already drawn.

6. Outcome questionnaires

Health complaints scale - The Health Complaints Scale consists of 12 somatic and 12 cognitive items answered on a 5 point Likert scale. Three somatic subscales (cardiopulmonary complaints, fatigue and sleep problems) and two cognitive subscales (health worries, disability feelings) can be identified. The questionnaire has been developed as an outcome measure in patients with coronary heart disease, and has demonstrated sensitivity to treatment in patients attending cardiac rehabilitation ²⁴.

MOS – General adherence: The questionnaire contains 4 general adherence questions asking whether the patient has complied with the doctor's suggestions and treatment plan and the ease with which the patient had adhered on a 6-point Likert scale (1: None of the time – 6: All of the time).³⁹

MOS – Adherence behaviors: This questionnaire contains 15 adherence behaviors for which the patients should answer on a 6-point Likert scale to what extent (1: None of the time – 6: All of the time) they have adhered to these disease specific adherence behaviors (e.g. cutting down on stress in life, try to socialize more, exercise more often, take medication).³⁹

Quality of life& health complaints (all measurement occasions)

Satisfaction with life (**SWLS**), quality of life (**WHOQOL-bref**), Health complaints (**HCS**), Angina symptoms (**SAQ**)

Table 1. Summary table questionnaire

	#items	Name Questionnaire	Ref.	Measurement occasions
Personality				
Neuroticism/ Extraversion	24	EPQ-NE	40	T0, T3
Type D	14	DS-14	32	T0, T1, T3
Optimism	10	LOT-R		T0, T3
Mindfulness	20	FFMQ	12	T0, T1, T3
Resilience	15	DRS		T0, T3
Cardiac self-efficacy	10	CSAQ	41	T0, T3, T4
Trait anger	10	STAQ		T0, T1, T2
Hostility	7	CMHS	42	T1, T3, T4
Mood				
Depression	32	PHQ-9 BDI-II	20,29	T0, T1, T2, T3, T4
Anxiety	7	GAD-7	26	T0, T1, T2, T3, T4
Negative mood state	6	GMS-12	43	T0, T1, T2, T3, T4
Positive mood state	6	GMS-12	43	T0, T1, T2, T3, T4
Emotion regulation				
Coping	48	CISS	44	T0, T1, T2, T3
Psychological mindedness	24	BIPM	37	T0, T2, T4
Worry	16	PSWQ	45	T0, T1, T2, T3, T4
Chronic stress				
Life events scale	28	Levens- gebeurtenissen	21	T0, T3, T4
Effort-reward imbalance	16	ERI	22	T0, T3, T4
Marital quality	6	MMQ6	23	T0, T3, T4
PTSD	22	SRiP		T0 T2
Outcomes				
Health complaints	22	HCS	24	T0, T1, T3, T4
Angina symptoms	7	SAQ-7	46	T0, T1, T3, T4
Quality of Life	26	WHOQOL bref	47	T0, T1, T3, T4
Behaviors				
Adherence	22	MOS adherence	39	T0, T1, T2, T3, T4
Decision making				
Shared decision making	9	SDM-Q-9		

6.1 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. However, their clinical data will remain in the standard of care PCI registry, because this is bound by law. The investigator can decide to withdraw a subject from the study for urgent medical reasons, i.e. if a participant is too ill to fill out questionnaires or have their blood drawn.

6.1.1 Specific criteria for withdrawal (if applicable)

Patients will be withdrawn from the study when the cardiologist negative advices on participation.

6.2 Replacement of individual subjects after withdrawal

Patients will be included until the number of participants is reached necessary to obtain the desired effect size with sufficient statistical power. So, if participants drop out or withdraw from the study, additional patients will be recruited.

6.3 Premature termination of the study

Criteria for premature termination of the study:
no one is willing to participate.

7. SAFETY REPORTING

7.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

We will record procedures (PCI, CABG), implantations (ICD, pacemaker), myocardial infarction (MI) and mortality for the first 10 years after inclusion.

7.2.2 Serious adverse events (SAEs)

As the current research proposal does not involve an intervention but is observational in nature, adverse events due to disease progression will only be recorded and will not be separately reported. All adverse events that occur in the current PCI population within the first year post-PCI will also be reported to the national PCI registry.

8. STATISTICAL ANALYSIS

Baseline characteristics will be described in means (SD) for continuous variables and in percentages (N) in case of categorized variables. Differences in baseline characteristics for example between participants that are and are not attending cardiac rehabilitation or between emotionally distressed and non-distressed participants are calculated using t-tests in case of continuous variables and using chi-square tests in case of categorized variables. When more than two categories are present, z tests will discriminate significant column differences, and appropriate Bonferroni corrections for multiple comparisons will be applied. Questionnaire scores will be calculated as described in the methods section above.

Missing data: If on a questionnaire a few items are missing (between 100-75% of items filled out), items will be imputed by replacing the missing score with that subjects mean score. This means that only 75% of the questions within a questionnaire need to be filled out to be able to compute a total score.

Answering the main objectives:

Prediction of outcomes	Multivariate logistic regression analysis and Cox proportional hazard models will be used to examine the long term predictive qualities of psychological and medical risk factors on complications, events, hospital admission and mortality.
Validation	Exploratory and confirmatory factor analysis and reliability statistics will be used to validate the ESC psychosocial screening instrument
Mechanisms	Multiple regression analysis, mixed linear modelling and path analysis using structural equation modelling will be used to examine the interrelations between the various potential biological and behavioral mechanisms explaining the link between psychological risk factors and cardiovascular prognosis. Cluster analysis will be used to identify different patient profiles over the course of time based on the prospective biological and psychological data.
Gender effects	Moderation analysis will be used to examine the moderating effect of sex and gender.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The PCI registry research project will be conducted according to the principles of the Declaration of Helsinki (2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO), Dutch data protection act (Wbp) and the Code of ethics for psychologists (2007).

9.2 Recruitment and consent

Patients will be recruited in the *Questionnaire study* when they are admitted to the TweekSteden hospital for an elective or subacute PCI. Beforehand (a couple of days to a week before admission),

when the Heart team has decided that a PCI is necessary, the patient will receive a letter from his/her cardiologist informing him/her on the PCI Registry study. The letter explains that there is a main study consisting of questionnaires only, and that there will be substudies in the future in which a patient can participate as well. Patients may give consent for the main study, but may also give consent for added substudies. After study information has been given by the cardiologist and the patient is deemed eligible by the cardiologist, patients will be recruited by a junior researcher (paid by NWO) together with a specialized PCI nurse that guides all patients during the period preceding the PCI. Patients will have 3-4 days to consider their participation, or can decide immediately. The patient information letter and the informed consent are attached as separate documents.

Acute PCI patients (patients that receive a PCI immediately after presentation at the ER with significant cardiac complaints or an MI) will be invited into the study after they have received the PCI, while still admitted at the hospital. Patients are informed about the study by their cardiologist or PCI nurse and receive an information letter and informed consent which they can return immediately or by mail in the week after the PCI. At the moment the patient has decided to participate, an email link is sent for the first questionnaire or the paper questionnaire is handed to them in hospital or sent by mail. For the blood sub study in the acute patients, participating patients need to provide consent when still in hospital because of the timing of blood sampling.

9.3 Benefits and risks assessment, group relatedness

This is a non-therapeutic observation study. There is only a limited risk to participation. Filling out questionnaires about psychological symptoms may induce people to contemplate their own mental health. Importantly, the question about suicide, which is included in the depression questionnaire, has been shown not to induce more suicide events (e.g.,⁴⁸). In case a person would answer that he/she is actively thinking about suicide, the coding will be broken, and the person will be contacted to offer help (e.g. contacting the GP for this person, or arranging a consultation with a psychologist).

The benefits of participation are that by implementing the psychosocial risk factor screening instrument, psychosocial issues may be identified sooner, and appropriate care may be initiated sooner. Moreover, participation of the cardiology department of the TweeSteden hospital in this PCI registry may induce better adherence to the PCI guidelines, as the registry asks the cardiologists and nurses to better registration of the post-PCI treatment phase (rehabilitation, diet, lifestyle advice).

9.4 Compensation for injury

We would like to ask for dispensation from the statutory obligation to provide insurance, because participating in the study is considered a minimal risk. A reasoned request is attached to this proposal as a separate document. In accordance with article 7, subsection 6 of the WMO Tilburg University has a liability insurance covering the research activities of its employees.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Upon entry in the study, participants will receive a study number. All data collected for the study, will use this subject number instead of the patient's name or hospital patient number. The study number consists of "CoRPS Project number"- "CoRPS Site number"-Study serial number" (xxxx-xxx-xxxx). Questionnaire data will be collected through CoRQuest, a digital questionnaire program, and medical

data will be recorded in a digital case record form. Digital data will be stored on a separate server using the patient's study number as a unique identifier and linking pin to connect questionnaire and medical data. All other documents on paper (e.g., signed informed consents, questionnaires filled out on paper) will be stored in the CoRPS research institute archive for 15 years.

10.2 Monitoring and Quality Assurance

Study quality monitoring takes place using a digital application that was built by Spits research support (Tilburg University). With the "Patient Management System" monthly queries will be ran on study inclusion and attrition. Also, the PMS will keep a record of the completion of measurements so that at any time an overview is present of the completeness of data at all measurement occasions as well as the percentage of missing data.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All significant amendments will be notified to the METC that gave a favourable opinion.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the study to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

10.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's visit. In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.6 Public disclosure and publication policy

The study design of the registry study and its substudies will be registered as an observational cohort study. The results from the current study will be published in international peer reviewed journals and will be presented at national and international conferences. Patients will be informed on the results of the study by a patient newsletter and by information on the CoRPS patient website (www.tilburguniversity.edu/corps).

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APPENDIX I - ESC Prevention guideline Psychosocial Risk Factor Screener

Name:

Patient ID:

What is your highest educational degree?

☐ University, Higher vocational

☐ Intermediate vocational

☐ Secondary education

☐ Primary education (or less)

What is your marital status?

☐ Married or living together

☐ Partner not living together

☐ Single

☐ Divorced, widowed

What is your work status?

☐ Working

☐ Pensioner

☐ Unemployed / In training

☐ Household work

Not at all Somewhat Pretty much Very much

11.1 Over the past 2 weeks, have you been bothered by any of the following problems?

Do you feel down, depressed, and hopeless?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you lost interest and pleasure in life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you, at times, suddenly feel fear or panic?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Are you unable to stop or control worrying?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you feel tired, or have a lack of energy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11.2 Lately, have you experienced any of the following stressors?

Do you feel burdened by your working conditions?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you receive insufficient appreciation for your work?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you lack a close confidant?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you have family problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you suffer from nightmares or recurrent unpleasant memories?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11.3 In general, how would you describe yourself?

Do you often feel anxious, irritable, or depressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you tend to take a gloomy view of things?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you find it hard to start a conversation because you don't know what to talk about?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you consider yourself to be a closed kind of person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you tend to bottle up your anger?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Are you bothered by outbursts of anger?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you find it hard to trust people?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do you feel that you often are told what to do by less knowledgeable people?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11.4 Have you experienced any of the following?

Did you experience 1 or more negative events in your life that still produce strong & negative feelings in the present?	<input type="checkbox"/> yes, namely.....
	<input type="checkbox"/> no
Have you ever been told you had a mental disorder (such as depression etc.) or were treated by a psychiatrist or a psychologist?"	<input type="checkbox"/> yes, namely.....
	<input type="checkbox"/> no

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