Official title of project: INvestigating Fear Of Recurrence as a modifiable Mechanism of behavior change to improve medication adherence in acute coronary syndrome patients (the INFORM Study)

NCT number of project: NCT03853213

Document date: 06/21/2019

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1. Study Purpose and Rationale

Acute coronary syndrome (ACS; myocardial infarction or unstable angina) is a leading cause of morbidity and mortality in the U.S., and survivors are at high risk for recurrent cardiovascular disease (CVD) events, particularly if they do not adhere to risk-reducing medications. Failure to take aspirin as prescribed is associated with 75% increased risk of recurrent CVD events or mortality,[1] and half of ACS patients are nonadherent to secondary risk medications by 1 year after the index ACS event. Emerging evidence suggests that posttraumatic stress disorder (PTSD) symptoms following ACS and other cardiovascular disease (CVD) are strongly associated with medication nonadherence, and ~50% of patients report symptoms.[2-4] Indeed, our pilot data suggest that those who are most distressed by a CVD event (as evidenced by PTSD symptoms) are also those least likely to behave in ways that would reduce the probability of CVD event recurrence.[5]

PTSD caused by a life-threatening medical event is reliably associated with heightened fear of CVD event recurrence.[6-8] We and others have proposed that ACS-induced PTSD symptoms may be distinct from PTSD due to stereotypical traumatic events such as combat or assault, because intrusive thoughts may be focused on fear of CVD event recurrence (FoR) in the future, rather than preoccupation with the past cardiac event.[9] Ironically, rather than promoting preventive health behaviors, FoR may be associated with worse medication adherence, as patients who develop PTSD symptoms report avoiding medications because they do not want to be reminded of their CVD risk.[10] It is possible that the small/distal perceived CVD benefit of adherence relative to the large/proximal psychological benefit of avoidance[10] may result in nonadherence. We now propose to determine whether FoR is a modifiable mechanism linking PTSD symptoms with nonadherence to aspirin for secondary prevention in ACS patients.

We will use the Science of Behavior Change (SOBC) experimental medicine approach to identify, measure, and influence FoR and related cognitive mechanisms (e.g., diminished future time perspective), and determine whether change in FoR is related to change in medication adherence. We will enroll N = 100 patients within 6 weeks of first presenting to the emergency department with suspected acute coronary syndrome who reported elevated early symptoms indicative of risk of developing PTSD (threat perceptions) at the time of their emergency department visit.[11] In all participants, we will measure FoR using the Concerns About Recurrence Scale (which we have adapted for ACS).[13] We will also measure future time perspective using an assay from the SOBC measures repository: the Future Time Perspective Scale,[14] to test their association with FoR and nonadherence. Prior to discharge, we will randomize patients to receive a computerized cognitive-affective FoR intervention [8 sessions (30 min/session; 2/week for 4 weeks)[13] or control task, to test whether the intervention reduces FoR. The brief intervention has successfully reduced FoR in cancer patients. It trains patients to attend away from threatening disease-related cues (e.g., looking away from the word recurrence and instead toward a neutral word such as categories) and to make benign interpretations of ambiguous, potentially disease-related information (e.g., fatigue reflects lack of sleep, not ACS recurrence). Finally, we will test whether the intervention (and/or improvement in FoR) is associated with greater electronically-measured adherence to aspirin or other heart medications, including non-aspirin antiplatelet, beta-blockers, or statins, in the 2 months after discharge.

Specific Aim 1: To measure FoR in ACS patients, and test its associations with ACS-induced PTSD, diminished future time perspective, nonadherence to medications, and lack of physical activity.

Specific Aim 2: To test whether a cognitive-affective intervention reduces FoR in ACS patients.

Specific Aim 3: To test whether patients randomized to the intervention are more adherent to aspirin in the 2 months after discharge for ACS, and secondarily, whether any intervention effect is explained by reduced FoR.

Exploratory Aim 1: We will test for off-target intervention effects on future time perspective, as well as the alternative mediation path through improvement in future time perspective.

Exploratory Aim 2: We will test whether the intervention is associated with greater increases in physical activity relative to the control group and whether this association is mediated by changes in FoR or future time perspective.

Half of ACS patients are nonadherent to secondary prevention medications within 1 year of their ACS event, and so are at increased ACS recurrence and mortality risk.[15] PTSD symptoms are associated with nonadherence after acute cardiovascular events, and our work suggests that FoR may underlie that association. This will be the first study to identify (and perhaps modify) cognitive/affective mechanisms of adherence behavior in patients at high risk for ACS recurrence and mortality. Physicians routinely magnify patients' FoR after acute life-threatening medical events to capitalize on the "teachable moment." This study may provide evidence for the opposite approach, as well as validated measures to assess FoR in CVD patients.

2. Study Design

We will enroll 100 English- and Spanish-speaking patients (50 intervention group, 50 control group) who recently presented to the ED of the New York Presbyterian Hospital (NYPH) with a probable admitting diagnosis of acute coronary syndrome (ACS). Specifically, eligible participants will be patients already enrolled in a separate approved protocol (IRB-AAAR7350: "Testing biopsychosocial mechanisms of the posthospital syndrome [PHS] model of early rehospitalization in cardiac patients") who presented to the NYPH ED with chest pain and an admitting diagnosis of non-ST-elevation myocardial infarction (NSTEMI) or unstable angina (UA). Prior to enrollment in that separate study, participants will have verbally confirmed with the caregiving physician that they were not active substance abusers, demented, and/or psychotic. Patients will *not* be eligible for the present study unless they indicated during the consent procedure for that separate protocol that they were willing to be contacted about participating in a different study. In terms of timing, patients who consented to the PHS study within the last 6 weeks (i.e., 42 days) will be potentially eligible for the present study.

The fundamental components of the study design are described below (see Procedure section for more details). One to three bilingual (English/Spanish) research assistants (RAs) assist in data collection at each session.

Study recruitment occurs primarily in the hospital after the potentially eligible patients (those currently enrolled in the separate protocol AAAR7350 and interested in learning more about other research studies) have been admitted to the hospital and transferred to an inpatient bed. For some patients, study recruitment may occur post-discharge, up to 6 weeks following participants' presentation to the Emergency Department when they enrolled in the PHS study. Research coordinators for the present protocol will approach these patients, introduce the study and begin the informed consent process. Consenting participants are randomized to the intervention or control condition and complete baseline measures for the present protocol at the pre-training session (i.e., Time 1). Participants are given an electronic tablet device and a brief training on its use at the end of or within several days of this baseline session. For the subset of patients who provide signed consent and the brief tablet training for this intervention study in the hospital but who are then discharged prior to this session, the Time-1 session is conducted by phone while the patients are at home. An additional subset of patients who consent to participate in this study will come to CUMC after hospital discharge to conduct the questionnaires and the brief tablet training of the pre-training session (i.e., Time 1) in person. All participants then complete 8 sessions of the training (intervention or control version) at home twice per week for 4 weeks using the tablet. During this time their adherence to a heart medication is monitored using eCAP devices that they receive during enrollment or in the mail. For participants currently prescribed aspirin but no other heart medication, their adherence to aspirin will be monitored using the eCAP devices. For participants *not* currently prescribed aspirin but who *are* currently prescribed a heart medication other than aspirin, such as a non-aspirin antiplatelet, a beta-blocker, a statin, or an antihypertensive medication, their adherence to this other heart medication is monitored using the eCAP devices. Within several days following the completion of the 4-week training, participants are then contacted by phone for the post-training session (i.,e., Time 2), during which they complete the same measures as completed at the Time-1 session. Then, participants return the tablet devices to CUMC researchers using pre-addressed envelopes/packages mailed to their homes. Finally, at 8 weeks after the Time-1 session, participants return the eCAP medication adherence monitoring devices to CUMC researchers also using pre-addressed envelopes/packages boxes.

Participants must meet inclusion and exclusion criteria, as specified below.

Inclusion criteria

(1) Age 18 years or older
(2) Fluent in English or Spanish
(3) A diagnosis of suspected acute coronary syndrome (ACS)
(4) Currently enrolled in the protocol titled "Testing biopsychosocial mechanisms of the posthospital syndrome [PHS] model of early rehospitalization in cardiac patients" (IRB-AAAR7350)
(5) Previously indicated "YES" to the following question in the consent form for the separate protocol (IRB-AAAR7350) in which they are enrolled: "I am willing to be contacted about other future research projects."
(6) Elevated Threat Perception score in emergency department (or, if not available, then elevated Recollected Threat Perception score in emergency department using a

separate post-emergency department questionnaire) flagged by automatic scoring (i.e., ≥ 8, the upper 75% of 1,000 ACS patients in a separate sample)
(7) Currently on a daily aspirin regimen prescribed by a doctor OR currently on a daily non-aspirin antiplatelet (e.g., Plavix), beta-blocker, statin, or anti-hypertensive regimen prescribed by a doctor
(8) Some comfort using technology such as electronic tablets or smartphones
(9) Time elapsed since emergency department visit at which they enrolled in the PHS study is less than 6 weeks

Exclusion criteria

(1) Deemed unable to comply with the protocol (either self-selected or by indicating during screening that s/he could not complete all requested tasks). This includes patients with a level of cognitive impairment indicative of dementia and patients with current alcohol or substance abuse
(2) Deemed to need immediate psychiatric intervention (that is, has to be hospitalized or have some other psychiatric intervention within 72 hours)
(3) Unavailable for follow-up. This includes patients with a terminal noncardiovascular illness (life expectancy less than 1 year by physician report) and those who indicate they are about to leave the United States
(4) Underwent a surgical procedure within the past 24 hours and/or is scheduled for a surgical procedure within the next 24 hours

The training sessions are administered by participants via the tablet devices twice per week for 4 weeks. The design of the training is described below separately for both conditions: intervention and control.

Cognitive-Affective Training (8 at-home sessions; 30 minutes each)

Cognitive bias modification for attention (CBM-A)

Intervention version: In this modified dot probe task,[26] CBM-A trials in the intervention are designed to reinforce attention away from ACS threat-related stimuli (e.g., "death," "heart attack") and toward neutral stimuli (e.g., "diets," "vacuum cleaner"). Threat-related and neutral word pairs are matched on approximate number of characters and frequency of use in English and Spanish, at a fourth grade reading level per the Flesch-Kincaid readability statistic. This task consists of 160 trials (130 training trials, 30 test trials). Each trial begins with one pair of threat-neutral words for 500 ms. Each word occupies either the top or bottom portion of the screen with randomized location. Next a target screen appears that consists of a single letter (E or F) appearing in either the top or bottom location. Participants' task is to respond as quickly and accurately as possible by tapping one of two buttons on the tablet screen to indicate whether they see E or F. For participants in the intervention group, in the 130 training trials of the task, the location of the target letter (i.e., top or bottom) is always the location previously occupied by the neutral word. The other 30 trials of the task are test trials that are randomly interspersed among the training trials. For half of the test trials, the location of the target letter is the location previously occupied by the threat-related word, and for the other half of the test trials, the location of the target

letter is the location previously occupied by the neutral word. Thus, participants in the intervention group are reinforced for attending to the neutral word and away from the threat-related word on 90.6% of trials (145/160).

Control version: For participants in the control group, in the 130 training trials of the task, the location of the target letter (i.e., top or bottom) is equally likely to be the location previously occupied by the threat-related word and the neutral word. The 30 test trials for the control group are identical to the test trials for the intervention. Example trial from intervention group (see above). Thus, participants in the control group are not reinforced for attending to either particular kind of stimuli. For each administration of the task, preferential attentional allocation toward threat-related information is assessed as the mean response time for test trials in which the target location is congruent with the threat-related word subtracted from the mean response time for test trials in which the target location is incongruent with the threat-related word. In this way, as a manipulation check, we will assess the extent to which attentional allocation to threat diminishes as a function of group and session (1-8) over the course of the 8 training sessions.

Cognitive bias modification for interpretation (CBM-I)

Intervention version: CBM-I trials are designed to train participants to appraise ambiguous information that is potentially related to ACS threat as benign. Each of 100 trials begins with a word or short phrase corresponding to either a threatening (e.g., "dying") or benign (e.g., "sleep") interpretation of a sentence that follows it (e.g., "You have been waking up tired recently"). On the next screen participants are asked to tap one of two buttons on the screen of the tablet to indicate "Yes" or "No" in response to the question "Was the word or phrase related to the sentence?" Participants in the intervention group receive positive feedback ("You are correct!") for rejected threat interpretations or for benign interpretations, and otherwise they receive negative feedback ("You are incorrect").

Control version: Participants are equally likely to receive positive or negative feedback for endorsing or rejecting threat interpretations or for endorsing or rejecting benign interpretations. For each administration of the task, the tendency to make threat interpretations is assessed as the proportion of threat endorsements (i.e., "Yes" responses) on trials with threat-related words, and the tendency toward benign interpretations is assessed as the proportion of benign endorsements on trials with benign words. Additionally, we will assess threat rejection time (i.e., mean speed of responding "No" on trials with sentences preceded by a threat-related word).

Measures

Fear of recurrence (FoR) of ACS. We have adapted the Concerns about Recurrence Scale (CARS)[13] for ACS. This multidimensional scale was originally designed to measure fear of recurrence of breast cancer. This adapted scale comprises 26 items evaluating three specific components of FCR. The health worries subscale evaluates fears about declining health (e.g., "I worry that a recurrence of a heart problem would threaten my physical health"). The role worries subscale evaluates fears about impaired relationships with other

people (e.g., "I worry that a recurrence of a heart problem would keep me from fulfilling my responsibilities"). The death worries subscale evaluates fears about mortality (e.g., "I worry that a recurrence of a heart problem would threaten my life"). Each item is rated on a Likert scale ranging from 0 (not at all) to 4 (extremely). A total score can be obtained for each subscale and for the total scale by summing the items. A higher score indicates higher levels of FoR.

Future time perspective. An exploratory aim of the study is to determine the relationships among FoR and medication adherence with future time perspective. Patients with cardiac-induced PTSD often report that their sense of the future is foreshortened, and prior conceptualizations of PTSD emphasized this sense.[7] This sense of a foreshortened future has been shown to strongly predict PTSD diagnosis in a population of patients with multiple sclerosis, and may be similarly associated with both PTSD and nonadherence in ACS patients.[16]

If PTSD, FoR, or both are also associated with diminished future time perspective, patients may value future life goals (e.g., maintain long-term heart health by taking aspirin daily) less than more immediate goals (e.g., avoid distressing reminders of past trauma and future mortality), with predictable consequences for health behaviors. Behavioral economics research suggests that diminished future perspective is associated with lower medication adherence among patients with hypertension and diabetes.[17] We will explore the associations among PTSD, FoR, and a measure from the SOBC measures repository that assesses time perspective; the 10-item self-reported Future Time Perspective Scale assesses the extent to which participants conceive of the future as relatively limited or open-ended.[14]

Medication adherence. We measure adherence to aspirin objectively using eCAPS (Information Mediary Corp., Ottawa, Canada). Medication bottles with these special caps automatically record the date and time of bottle openings. Medication adherence across a unit of time (e.g., 1 week, 1 month) is computed as the proportion of days that participants took the correct number of aspirin pills. If patients are taking aspirin and other heart medications (i.e., non-aspirin antiplatelets, beta-blockers, statins, or antihypertensives), then the aspirin will be the heart medication they will place in the eCAP bottle to be monitored. However, if patients are taking other heart medications (i.e., non-aspirin antiplatelets, beta-blockers, statins, or antihypertensives) but *not* aspirin, then they will choose which one medication (either a non-aspirin antiplatelet, beta-blocker, statin, or antihypertensive) to put in the eCAP bottle to be monitored.

Threat Perceptions. In a separate protocol we measure perceptions of threat, which are very early indicators of PTSD symptoms at the emergency department.[11] This measure is used as part of the eligibility criteria (see above).

Context sensitivity. We measure participants' ability to identify information about stressful situations that is helpful for the successful and flexible regulation of distress. The Context Sensitivity Index (CSI) presents hypothetical scenarios and asks participants to answer questions about them (e.g., "How much control do you have over what happens next?").[12]

3. Statistical Procedures

Analysis Plan

Specific Aim 1.
To measure FoR in ACS patients, and test its associations with ACS-induced PTSD, diminished future time perspective, and nonadherence to medications.
We will test the extent to which the hypothesized measures of the behavior change mechanisms in question (FoR, future time perspective) are intercorrelated in ACS patients with elevated acute stress symptoms. First, to test convergent validity, we will assess zero-order correlations among these measures. Specifically, we predict that—across both groups at Time 1 before the intervention—higher FoR will be associated with lower future time perspective (i.e., lower FTPS). Second, we will test whether higher FoR is associated with higher threat perception symptoms and overall lower proportion of days adherent to aspirin. Third, due to the within-subjects design, we will also assess test-retest reliability from Time 1 to 2, both across and within groups. In this way we will ensure that we have valid and reliable measures of our proposed mechanisms of behavior change.

Specific Aim 2.
To test whether a cognitive-affective intervention reduces FoR in ACS patients.
We will conduct a univariate ANOVA to assess the effect of the four-week intervention on pre-to-post change in FoR, the proposed target mechanism. Prior intervention research in cancer patients showed a small to moderate effect size of a cognitive-affective intervention on FoR symptoms (Hedge's g for difference in health worries from pre- to post-intervention = 0.35). In separate unadjusted tests with pre-to-post change in FoR (and in an exploratory test of future time perspective) as the outcome, we will enter group (intervention, control) as the predictor. We will repeat the tests adjusting for factors that may explain variance in health behavior, including demographic information (age, sex, race, ethnicity), medical severity assessed by GRACE risk score[18] and Charlson comorbidity index,[19] and depressive symptoms assessed by PHQ-8 score.[20]

Specific Aim 3.
To test whether patients randomized to the intervention are more adherent to aspirin in the 2-month monitoring period within the first several months after their suspected ACS event, and secondarily, whether any intervention effect is explained by reduced FoR.
We will test this mediational hypothesis using conditional process modeling with the PROCESS macro in SPSS.[21] Although we will likely have insufficient power to test the question definitively, the results will inform whether a future larger trial is warranted. The behavioral outcome in the model is heart medication adherence from the eCAP data: mean proportion of adherent days in the 2-month monitoring period that occurs within several months after hospital discharge. The predictor is group (intervention, control). The mediator is pre-to-post change in FoR from Time 1 to 2. For a secondary analysis, we will test the outcome as the magnitude of the slope of change in weekly proportion of adherent days during the 2 months. We will evaluate whether there is a significant indirect effect that supports the notion that the intervention vs. the control training engaged the target mechanism in such a way that changes in the target predicted improved heart medication adherence over the month-long intervention.

Exploratory Aim 1.
We will test for off-target intervention effects on future time perspective, as well as the alternative mediation path through improvement in future time perspective.
The test will be structured as for Specific Aim 3 but with pre-to-post change in future time perspective as the tested mediator.

Exploratory Aim 2.
We will test whether the intervention is associated with greater increases in physical activity relative to the control group and whether this association is mediated by changes in FoR or future time perspective.
The test will be structured as for Specific Aim 3 and Exploratory Aim 1 but with physical activity as the tested behavioral outcome measure instead of medication adherence.

Power analysis.
In prior research with N = 97 at Time 1 using a similar intervention in cancer patients, a moderate effect size (Hedges g = 0.54) was found for differences in FoR between the intervention (n = 64) and control (n = 36) groups after 3 months and a somewhat smaller effect size (Hedge's g = 0.35) immediately after the 1-month intervention.[13] Using G*Power 3.1,[22] we tested a range of effect sizes for two levels of power. We determined that the present study is conservatively powered to change FoR in a fixed-effects one-way ANOVA with an effect size *f* of 0.35 or larger with a sample size of N = 100 (50 intervention, 50 control), given alpha = .05 and an intention-to-treat design in which missing data due to attrition are handled with multiple imputation.

4. Study Procedures

Patients will be considered for enrollment in the present study who are currently enrolled in AAAR7350 (the PHS study), who signed consent for AAAR7350 within the last 6 weeks (i.e., 42 days), who have indicated they are willing to hear about other research studies, and who have an Elevated Threat Perception score. Consent will be obtained using an IRB-approved consent form.

Pre-training/Time 1: For patients consenting to the study in the hospital, the pre-training session ideally occurs at this same visit. The RA will assess the potential mechanisms of behavior change verbally. At the end of this session, each patient will be given a tablet and an eCAP bottle with a brief explanation of their use. The estimated duration of this session is 45 minutes, including the consent process, questionnaires, and the brief training in the use of the tablet. A subset of patients will complete the consent process and receive the devices (eCAP bottle, tablet) with a brief training in the hospital and will then separately complete the questionnaires verbally by phone within several days. A separate subset of patients will complete the Time-1 session at CUMC sometime after hospital discharge but before 6 weeks (i.e., 42 days) have elapsed from the time of consent to the protocol AAAR7350.

Training phase: Random group assignment to the intervention or control group will be determined in a double-blind way by the programmed tasks on the tablet for each participant.

Participants are asked to complete 8 at-home 30-minute intervention sessions (both CBM-A and CBM-I tasks are programmed to occur sequentially in one session). The schedule of sessions is 2 times per week. Participants will receive brief, automated text messages 2 times each week reminding them to complete these sessions. Phone calls will be conducted instead of text messages for participants without text message capability or for particular scheduled training sessions when participants do not respond to the text reminders.

Post-training/Time 2: A clinical coordinator will administer the measures by phone interview. Participants who prefer a home visit may complete the session in person and return their tablet to the interviewing clinical coordinator at that time. The estimated duration of this session is 45 minutes. All other participants will return their tablets and eCAP bottles via mail: one pre-addressed envelope/ package for the return of the tablet at 4 weeks after the Time-1 session and soon after completion of the Time-2 session and one separate pre-addressed envelope/package for the return of the eCAP bottle at 8 weeks after the Time-1 session.

Monetary compensation is administered via pay card in two installments. In the first installment of monetary compensation, participants receive $20 at Time 1. Regarding the second installment of monetary compensation, it is structured such that participants are incentivized to return their devices with complete data. They receive $5 for completing the 1st at-home tablet tasks session, $5 for the 2nd, $5 for the 3rd, $5 for the 4th, $10 for the 5th, $10 for the 6th, $20 for the 7th, and $20 for the 8th tablet tasks session. They receive $20 for completing the Time 2 interview. The second study compensation is contingent upon return of the tablet following Time 2. Finally, in the third study compensation, participants receive $20 for returning the eCAP device. Thus, total study compensation for participants who complete all sessions is $140 ($20 in first installment + up to $100 in second installment + $20 in third installment).

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