American Psychological Association
Society for HEALTH PSYCHOLOGY
Health Psychology

ISSN: 0278-6133
2020, Vol. 39, No. 9, 736–744
http://dx.doi.org/10.1037/hea0000853

Intervening on Fear After Acute Cardiac Events: Rationale and Design of the INFORM Randomized Clinical Trial

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Objective: Many acute coronary syndrome (ACS) patients are nonadherent to cardiovascular medications despite their known benefits for lowering risk of recurrent cardiovascular events. Research suggests that greater cardiac-related fear of recurrence (FoR) may be associated with higher nonadherence to cardiovascular medications and avoidance of physical activity. We aim to test the effect of an intervention that targets FoR as a potentially modifiable mechanism underlying nonadherence to recommended health behaviors among patients with suspected ACS. ***Method:*** The INFORM trial ("INvestigating Fear Of Recurrence as a modifiable Mechanism of behavior change to improve medication adherence in acute coronary syndrome patients") is a double-blind, parallel-group randomized clinical trial. It compares an 8-session, at-home, electronic tablet-delivered, cognitive bias modification training (CBMT) intervention with a sham control. Patients who experience high perceived threat at the time of presentation to the emergency department (ED) with a suspected ACS are enrolled and randomized within 6 weeks of their ED visit. The primary outcome, FoR, is measured by the adapted Concerns about Recurrent ACS Scale. The trial also tests the intervention's effect on a potential mechanism of health behavior change that is inversely correlated with fear: an expansive future time perspective. Additional outcomes include electronically measured adherence to a cardiovascular medication and self-reported physical activity. ***Conclusions:*** This study takes a mechanistic approach to addressing the dangerous problem of poor health behaviors after ACS. The trial will test whether targeting FoR or future time perspective by CBMT is a promising approach to improving nonadherence after ACS.

Keywords: acute coronary syndrome, fear of recurrence, randomized clinical trial, cognitive bias modification, medication adherence

Supplemental materials: http://dx.doi.org/10.1037/hea0000853.supp

Nonadherence to cardiovascular medications is a serious problem among patients with cardiovascular disease (Bezin et al., 2014; Bitton, Choudhry, Matlin, Swanton, & Shrank, 2013; Ho, Bryson, & Rumsfeld, 2009). Approximately 40% of patients demonstrate poor implementation of their medication regimens, typically defined as taking less than 80% of prescribed doses (Chow-

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We extend gratitude to the INFORM participants for taking part in the study. We thank co-investigators Joseph E. Schwartz and Donald Edmondson for shaping the research questions and statistical approach, Wendy Lichtenthal for sharing the intervention stimuli for cancer patients, and Gabriel J. Sanchez, Alison R. Trainor, and Gaspar J. Cruz for helping to adapt the intervention and fear of recurrence measure for a cardiac population. The authors declare no financial or other conflicts of interest.

This study is supported by the National Institutes of Health (NIH) Science of Behavior Change Common Fund Program through an award administered by the National Heart, Lung, and Blood Institute to Jeffrey L. Birk (R21HL145970). Ian M. Kronish (R01HL123368) and D. Edmondson (R01HL128497) are supported by awards from the National Heart, Lung, and Blood Institute. The NIH was not directly involved in study design, data collection, data management, data analysis, writing, or submission of the baseline article.

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dhury et al., 2013). Failure to engage adequately in this critical health behavior carries severe consequences. Whereas inadequate adherence to cardiovascular medications is associated with an increase of over 50% in the incidence rate ratio of adverse cardiovascular events, adequate adherence is associated with a 35% reduced risk of all-cause mortality, adjusting for relevant clinical characteristics (Chowdhury et al., 2013). Addressing this behavioral problem is complex as reasons for nonadherence are numerous (Voils et al., 2012) and vary widely among patients (Cornelius, Voils, et al., 2018).

For a substantial subset of cardiac patients, negative emotions (e.g., fear, distress) constitute one important reason for missing or even deliberately avoiding their heart medications (Cornelius, Voils, et al., 2018; Husain, Edmondson, Kautz, Umland, & Kronish, 2018). This link between distressing emotion and nonadherence raises the question of whether physicians should aim to minimize or amplify a cardiac patient's fear after a frightening medical event such as a suspected heart attack. On the one hand, higher perceived threat and fear of future cardiac events may promote engagement in health behaviors, such as medication adherence (Lawson & Flocke, 2009). This notion that a scary acute coronary syndrome (ACS) can be a motivating "wake-up call" or "teachable moment" is supported by research showing that hospitalization after myocardial infarction is associated with improvement in adherence to statin medications relative to hospitalization for another reason among previously nonadherent patients (Kronish, Ross, Zhao, & Muntner, 2016). On the other hand, if fear is intense, it may prevent this teachable moment (McBride, Emmons, & Lipkus, 2003) and even worsen health behaviors instead. Indeed, high emotional distress about health is associated with lower medication adherence (DiMatteo et al., 1993), and posttraumatic stress disorder (PTSD) symptoms are associated with heart medication nonadherence (Kronish, Lin, Cohen, Voils, & Edmondson, 2014).

If fear indeed worsens medication adherence, this effect may pertain not only to preexisting psychiatric conditions (e.g., PTSD symptoms due to a prior, nonmedical trauma) but in addition—and perhaps *especially*—to distress caused by the cardiovascular condition that originally necessitated the heart medication. Strong fear of imminent death during ACS events is relatively common and predicts greater likelihood of developing lingering symptoms of anxiety and PTSD (Gander & von Känel, 2006; Whitehead, Strike, Perkins-Porras, & Steptoe, 2005). Similar to PTSD due to *any* cause (Kronish, Edmondson, Li, & Cohen, 2012; Kronish et al., 2014), these ACS-induced PTSD symptoms are also associated with poorer medication adherence (Shemesh et al., 2004). Indeed, ACS patients with high versus low cardiac-induced PTSD symptoms are more likely to report that they avoid their heart medications because they do not like to be reminded of their cardiac events (Husain et al., 2018).

Physical activity is another cardioprotective health behavior (Warburton, Nicol, & Bredin, 2006) that may be counterintuitively reduced among ACS patients with high fear. ACS patients with high versus low ACS-induced PTSD symptoms report that physical activity reminds them of their cardiac risk, and that they avoid physical activity because they fear it will cause a recurrent heart attack (Monane, Sanchez, Kronish, Edmondson, & Diaz, 2018). Thus, this growing body of evidence suggests that ACS-related fear about future risk for recurrent events may threaten cardiovascular health by worsening key preventive health behaviors.

Although FoR has been identified as a mechanism that may drive poor health behaviors in this cardiac population, the evidence is not yet definitive on this point for two reasons. First, the existing evidence concerns relatively broad constructs such as ACS-related PTSD symptoms rather than specifically fear of recurrent cardiovascular events. Second, the evidence is correlational, thereby precluding causal inferences. Thus, to determine whether cardiac-related FoR is a mechanism underlying nonadherence—and thus an appropriate target for adherence interventions—a more specific measure of fear of future acute cardiac events is needed, and this measured construct should be capable of being experimentally reduced via an intervention. Once a potent intervention is identified for reducing cardiac-related FoR, then one can test whether this same intervention results in improved adherence and whether this improvement is mediated through changes in fear. This approach to mechanism-focused adherence intervention testing is consistent with the experimental medicine approach espoused by the NIH's Science of Behavior Change (SOBC) initiative (Sumner, Beauchaine, & Nielsen, 2018).

Like FoR, future time perspective is a psychological construct that may influence health behaviors of cardiac patients who are concerned about impending, potentially lethal heart attacks. *Future time perspective* refers to a conception of one's own future as being relatively open-ended instead of limited in scope (Lang & Carstensen, 2002). Patients with high cardiac-induced psychological distress often report as one component of that distress that their sense of the future is foreshortened (von Känel et al., 2011), which has been shown to predict PTSD diagnosis in a population of patients with multiple sclerosis (Chalfant, Bryant, & Fulcher, 2004). Therefore, a diminished future time perspective may be similarly associated with psychological distress and high FoR in ACS patients. Indeed, interventions that reduce FoR in these patients may also expand future time perspective, which is itself part of the SOBC measures repository, a resource that tracks the scientific progress of measures of putative mechanisms underlying behavior change (The Science of Behavior Change, 2019). If high FoR covaries with diminished future time perspective, fearful patients may value future life goals such as maintaining long-term heart health by taking aspirin daily less than more immediate goals such as avoiding distressing reminders of past trauma and future mortality, with predictable consequences for health behaviors. Diminished future perspective is associated with lower medication adherence among patients with hypertension and diabetes (Sansbury, Dasgupta, Guthrie, & Ward, 2014).

This project takes a mechanistic, empirical approach to identify whether FoR should be a target for intervention development relevant to health behaviors in ACS patients. Given that interventions to improve medication adherence have been largely unsuccessful (Nieuwlaat et al., 2014), open-science research identifying and testing hypothesized mechanisms by which adherence may be changed via intervention is highly needed. For the aforementioned reasons, this study tests whether FoR should serve as one such mechanism aiming to improve adherence to medications. Given that similar mechanisms may underlie nonadherence to other health behaviors, this project will also explore the effect of the intervention on physical activity.

Cognitive bias modification training (CBMT) represents a promising approach for targeting FoR in ACS patients. CBMT aims to modify biased patterns of cognition in which people prioritize attention to negative information and interpret ambiguous or neutral information as threatening (MacLeod & Mathews, 2012). CBMT has been shown to shift habitual attentional allocation away from threat (Bar-Haim, 2010), change people's tendency to interpret ambiguous information in a more benign way (Menne-Lothmann et al., 2014), and reduce anxiety symptoms (Jones & Sharpe, 2017). Recently, CBMT has been shown to lastingly reduce FoR among cancer patients who initially reported at least some elevation in fears of cancer recurrence (Lichtenthal et al., 2017) by training attention away from threat-related stimuli (e.g., "biopsy") and toward neutral stimuli (e.g., "ankles"). Similarly, for ambiguous scenarios (e.g., "You have lost your appetite for a few hours"), they trained benign (e.g., "full") rather than threatening (e.g., "metastases") interpretations. Lichtenthal and colleagues found that cancer patients' health worries decreased more substantially from baseline to a 3-month follow-up session in the intervention versus the control group. As described below, we adapted CBMT to address cardiac-relevant concerns for the present study.

The study has three aims. The first aim is to test whether a tablet-based CBMT intervention influences putative fear-based mechanisms of health behavior change in patients with suspected ACS whose perception of threat is high at the time of ED presentation. The second aim is to determine the extent to which the two potential mechanisms of behavior change—FoR and future time perspective—are each associated with health behaviors. The third aim is to explore whether the intervention improves medication adherence or physical activity and whether any such beneficial effects are mediated by reductions in FoR or increases in future time perspective. The first aim is the study's primary focus, and the latter two aims will provide additional results that can inform the development of a larger trial to improve health behaviors in cardiac patients. Figure 1 presents the conceptual model of health behavior change that underlies the INFORM study's aims.

Method

Design Overview

This study is a single-center, double-blind, parallel-group randomized clinical trial conducted with The Trustees of Columbia University in the City of New York as the sponsor. The CONSORT statement will be used in the reporting of study results for this clinical trial (Boutron, Moher, Altman, Schulz, Ravaud, & the CONSORT Group, 2008; Schulz, Altman, Moher, & the CONSORT Group, 2010). Participants are English- and Spanish-speaking patients who recently presented with a suspected admitting diagnosis of ACS to the ED of the NewYork-Presbyterian Hospital at Columbia University Irving Medical Center (NYP-CUIMC) in New York, New York, in an urban setting characterized by a diverse, largely Hispanic population. Eligible participants report some fear related to their condition as measured by threat perceptions at their ED visit. Participants are randomly assigned (1:1) to compare CBMT (eight 30-min sessions over 4 weeks) and sham control on FoR (primary outcome), future time perspective, medication adherence, and physical activity. Supplemental Figure S1 in the online supplementary materials shows the timetable of procedures.

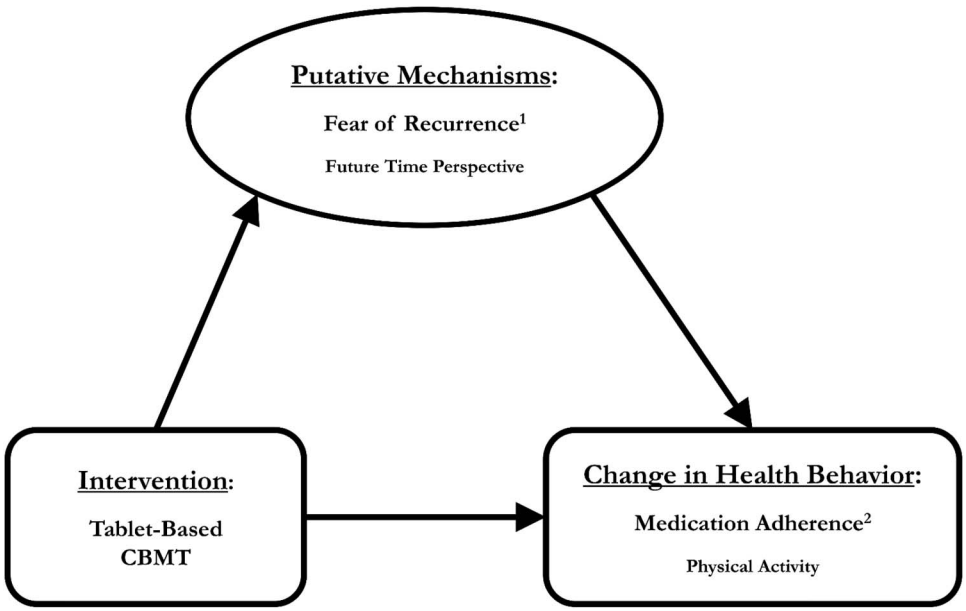

Figure 1. The conceptual model for INFORM. High fear of recurrence and low future time perspective are proposed mechanisms of poor health behaviors among patients with suspected acute coronary syndrome. The tablet-based intervention targets these mechanisms in this randomized clinical trial. CBMT = cognitive bias modification training. [1] Fear of recurrence is the study's primary outcome. [2] Medication adherence is the study's health behavior of interest.

Intervention Development

We adapted CBMT for ACS patients by incorporating fears specific to ACS. The content of the attention portion of the intervention focuses on cardiac-related threat (e.g., heart attack), and the interpretation portion focuses on somatic and cognitive symptoms that are ambiguous and may be interpreted as either threatening or benign (e.g., elevated heart rate after climbing stairs, inability to concentrate). The creation of cardiac-related content for the adaptation process was conducted with a five-person team of four experienced clinical coordinators under the direction of the principal investigator. The stimuli were created via the following steps: (a) generation of an initial list of potential stimuli (words, phrases, and sentences) based on a review of the literature about common fears after ACS (e.g., Steptoe et al., 2011; Whitehead et al., 2005) and group discussions of somatic and mental symptoms, thoughts, and experiences common to cardiac patients, including a consideration of all potentially relevant stimuli used in the CBMT developed for reducing breast cancer FoR (Lichtenthal et al., 2017); (b) independent quantitative rating of of all items on their appropriateness (e.g., sufficiently threatening, sufficiently benign), unambiguous meaning, and accessible language level; (c) creation of an averaged summary score that was used to select items with the highest such scores across all five raters; and (d) revision of those ranked stimuli based on ensuring that a variety of fear-relevant domains were adequately represented (i.e., threatening physical sensations, symptoms following exertion, alarming mental symptoms, scary thoughts, and frightening emotions) as well as approximate matching of the following characteristics for the paired stimuli in the attention task: number of words, approximate number of characters, and frequency of real-world linguistic use.

Eligibility

In observational research involving recruitment of patients with suspected ACS from the ED, the majority of patients are ultimately ruled out for ACS after their initial work-up at the ED (Birk et al., 2019). Nevertheless, somewhat surprisingly, patients with confirmed ACS and patients who rule out for ACS experience similar levels of psychological distress related to the event (Kronish et al., 2018) and show nearly identical trajectories of PTSD-like symptoms extending out to 12 months after their ED visit (Meli, Birk, Edmondson, & Bonanno, 2020). Thus, because preventing nonadherence is imperative for any patients who are prescribed a cardiovascular medication, because patients with suspected ACS often have high fear regardless of their subsequent diagnosis, and because CBMT is most effective for emotionally symptomatic people (Menne-Lothmann et al., 2014), the INFORM study recruits medicated adult patients with suspected ACS who report initially elevated fear.

Inclusion criteria are the following: (a) age 18 years or older; (b) diagnosis of suspected ACS; (c) elevated threat perception on the ED threat perception scale (Cornelius, Agarwal, et al., 2018; i.e., score $\geq$8, the upper 75% of 1,000 ACS patients in a separate sample); and (d) currently prescribed at least one cardiovascular medication (i.e., antiplatelet, antihypertensive, or statin). In addition, all participants (e) are currently enrolled in the protocol at NYP-CUIMC titled "Testing Biopsychosocial Mechanisms of the Posthospital Syndrome [PHS] Model of Early Rehospitalization in Cardiac Patients" (an ongoing 12-month observational cohort study of suspected ACS patients); and (f) previously indicated that they are willing to be contacted about other future research projects. Patients are excluded if they are (a) not fluent in English or Spanish; (b) lack comfort using technology such as electronic tablets or smartphones; (c) deemed unable to comply with the protocol (e.g., cognitive impairment indicative of dementia, current alcohol or substance abuse); (d) deemed to need immediate psychiatric intervention (i.e., need for hospitalization or psychiatric intervention within 72 hr); (e) unavailable for follow-up (e.g., a terminal noncardiovascular illness with life expectancy less than 1 year by physician report, imminent departure from the U.S.); or (f) underwent a surgical procedure within the past 24 hr or are scheduled for a surgical procedure within the next 24 hr. Potential participants are not excluded for taking part in concomitant care related to their medical condition(s) or in other interventions.

Randomization, Allocation, and Blinding

A data team member generates the random sequences in SAS software (Version 9.4) separately for English- and Spanish-speaking participants using a randomization schema with stratified permuted blocking techniques (Broglio, 2018). The randomization was stratified by language for a practical reason: tablets must be preprogrammed with the relevant tasks in a particular language before the next eligible participant's language can be known. These allocation sequences are concealed using a password-protected electronic file from all study participants, the principal investigator, all coinvestigators, all non-data-team study staff who interact with participants, and the study statistician. A data team member implements the allocation sequences by loading the assigned script for the relevant task condition (e.g., English-version intervention) onto the next available tablet according to the order specified. Tablets with English and Spanish versions of the tablet tasks are prepared in advance of the Time 1 sessions for the next eligible English- and Spanish-speaking study participants, respectively. Thus, although clinical coordinators enroll participants, a data team member effectively assigns participants to groups. All versions of the E-Prime 3 software scripts that run these tasks have identical names to conceal group assignment to study personnel. In addition, only the run-time version of the script is stored on each tablet such that the stimulus contingency tables that underlie group membership cannot be viewed even if a person were to access the script. All blinded participants and study staff remain blinded until after the completion of data collection for the entire study. The only exceptions are when breaking the blind may benefit a participant's health (e.g., a participant reports increased psychological distress related to the tablet tasks).

Recruitment, Enrollment, and Informed Consent

Suspected ACS patients are approached in the CUIMC-NYP ED and enrolled in the separate PHS protocol (see Eligibility section). Study coordinators then approach potential participants for INFORM recruitment in person or by phone within six weeks after their initial ED visit at which time they complete the informed consent procedure and tablet demonstration. Participants are informed that they can request to discontinue the study at any time and that their study participation may be terminated at the investigator's discretion (e.g., if they cannot be adequately trained to do

the tablet tasks). Each participant who consents to participate is given the tablet corresponding to their randomly assigned group and preferred language.

Three strategies were used to increase the research team's ability to reach the target enrollment in a timely way. First, the cutpoint for the inclusion criterion regarding the ED threat perception total score was set to increase the number of eligible patients. Second, a wide range of cardiovascular medications was allowed. Third, participants could begin the study beyond the initial hospitalization period up to 6 weeks after hospital discharge.

Intervention

Participants in the intervention group complete two tasks targeting fearful patterns of attention and interpretation, each repeated eight times over the course of 4 weeks (twice-per-week sessions; 16 tasks total). The first task is CBMT for attention. It is designed to reinforce attention away from ACS threat-related stimuli (e.g., "death," "chest pain") and toward neutral stimuli (e.g., "curve," "barn doors"). This task consists of 160 trials: 144 training trials and 16 randomly interspersed test trials. Each trial begins with one pair of threat-neutral words presented for a duration randomly jittered between 1,000 and 1,500 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*. A blank screen is then presented for a duration randomly jittered between 350 and 650 ms. Finally, each trial ends with a feedback screen lasting 1,000 ms for positive feedback ("Correct!!") and 2,000 ms for negative feedback ("Incorrect"). In the 144 training trials of the intervention version of the task, the target letter (i.e., top or bottom) is always in the location previously occupied by the neutral word, thereby training participants to attend away from the threat-related cardiac information. The other 16 trials of the task are test trials that are randomly interspersed among the training trials. These test trials have a fully balanced contingency such that the location of the threat word is entirely *non*informative regarding the subsequent location of the target stimulus. That is, 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 95% of trials (i.e., 152/160). Supplemental Figure S2 in the online supplementary materials shows schematic example trials for the attention task.

The second task is CBMT for interpretation. It is designed to train participants to appraise as benign information that is potentially related to ACS threat but is actually ambiguous. This task consists of 100 trials: 90 training trials and 10 randomly interspersed test trials. Each trial begins with the 1,750-ms presentation of a word or short phrase corresponding to either a threatening (e.g., "dying") or benign (e.g., "sleep") interpretation of a sentence (e.g., "You have been waking up tired recently") that follows the word or short phrase. Participants are asked to tap one of two buttons on the tablet screen to indicate "related" or "not related" in response to the question "Was the word or phrase RELATED or NOT RELATED to the sentence?" After a brief blank screen, with a randomly jittered duration of 350 ms to 650 ms, participants receive feedback. In the 90 training trials of the intervention version of the task, positive feedback ("You are correct!") is given for rejected threat interpretations and for benign interpretations, and otherwise negative feedback ("You are incorrect") is given. The other 10 trials of the task are test trials that are randomly interspersed among the training trials. These test trials are designed to have a fully balanced contingency such that the feedback is entirely *un*related to participants' choice to endorse or reject threat or benign interpretations (five trials with feedback reinforcing threat-consistent interpretations, five trials with feedback reinforcing neutral-consistent interpretations). Thus, participants in the intervention group are reinforced for choosing the nonthreatening interpretation on 95% of trials (i.e., 95/100). Supplemental Figure S3 in the online supplementary materials shows schematic example trials for the interpretation task.

Comparison: Control Group

Akin to the intervention group, participants in the sham control group complete two tasks, each repeated eight times over the course of four weeks (i.e., 16 tasks total). In this case, however, CBMT for attention is designed *not* to train attention toward or away from threatening or neutral information, and CBMT for interpretation is designed *not* to train the interpretation of information as either threatening or benign. This sham control condition is achieved by setting the cue-target and response-feedback contingencies for training trials in the attention and interpretation tasks, respectively, to be perfectly balanced (i.e., equal likelihood of targets appearing in cue locations of threat and neutral for the attention task, equal likelihood of positive and negative feedback regardless of participant's response for the interpretation task).

Study Timetable

The study timeline is presented in Supplemental Figure S1 in the online supplementary materials. The baseline/Time 1 session occurs either in hospital within several days of the patient's visit to the ED or, if not possible before hospital discharge, then at a separate visit within 6 weeks (i.e., ≤42 days) of the ED visit. All participants must complete a hands-on demonstration of the tablet tasks and practice opening a demonstration eCAP medication bottle in the presence of a study coordinator. Participants complete the baseline questionnaires at this session. At the session's end or shortly thereafter, participants are given their assigned tablet and eCAP medication bottle for home use. The 4-week training phase begins the day after the Time 1 session. To increase participant retention and adherence to the tablet sessions, participants are reminded to complete biweekly sessions by phone or short electronic text messages sent via Qualtrics. Following discharge, coordinators confirm medication prescribed to be used in the eCAP medication bottle. The posttraining/Time 2 session is conducted with participants by phone or in person. Participants complete a second set of questionnaires and return the tablets either by FedEx mail or in person. At Time 3, eight weeks after the Time-1 session, participants return the eCAP devices and exit questionnaires, either by USPS mail or in person. For participants who discontinue the

study or do not follow protocol (e.g., sometimes completing just a subset of trials of the tablet tasks), all available data that are relevant to the study's aims will be analyzed.

Outcome Measures

Primary outcome.

FoR (assessed at Time 1 and Time 2). FoR is measured using the 19-item Concerns About Recurrent ACS Scale adapted for ACS from a measure used to assess FoR in patients with breast cancer (Vickberg, 2003). This adapted scale measures health worries, role worries, and death worries related to recurrence of an ACS event. Similar to the intervention adaptation, the self-report scale items were adapted via discussions of the five-person team regarding ACS-relevant concerns. Because of the similar fears for cancer and for ACS, the changes were relatively few. First, relative to the original scale, the seven items related to the womanhood worries subscale were dropped due to their relevance to breast cancer rather than ACS. Second, three items were changed as follows: (a) "Require chemotherapy" was replaced with "Require a sudden return to the emergency room"; (2b) "Require radiation treatment" was replaced with "Require a serious medical procedure such as having a cardiac stent implanted"; and (c) "Mean losing my breast(s)" was replaced with "Mean getting a permanent scar on my chest." Psychometric properties of the measure will be tested: internal consistency reliability, convergent validity with related measures (e.g., threat perceptions in the ED), and discriminant validity with less closely related measures (e.g., PTSD symptoms, depressive symptoms). Concerning the primary focus of Aim 1 (see above), the study will test whether there is a larger Time 1 to Time 2 reduction in Concerns About Recurrent ACS total scores for the intervention group relative to the control group.

Secondary outcomes.

Future time perspective (assessed at Time 1 and Time 2). This secondary mechanistic target of the intervention is measured using the 10-item Future Time Perspective scale (Lang & Carstensen, 2002) that measures participants' perceptions of their own futures as either limited (lower scores) or expansive (higher scores). The study will test whether there is a larger Time 1 to Time 2 increase in Future Time Perspective total scores for the intervention group relative to the control group.

Proportion of days correct dosing (assessed for 8 weeks starting after Time 1). Implementation of the medication regimen is measured by electronically recorded pill bottle openings (Vrijens et al., 2012) using the eCAP device (Information Mediary Corp., Ottawa, Canada). The measure is operationalized as the proportion of days monitored with correct number of doses taken during the eight weeks of electronic monitoring.

Self-reported extent of medication nonadherence (assessed at Time 2). The self-reported scale called the Extent of Nonadherence Scale measures how often participants do not take their prescribed medication in the prior seven days (Voils et al., 2019).

Physical activity (assessed at Time 1 and Time 2). The seven-item International Physical Activity Questionnaire will be used to measure the extent to which participants engaged in physical activity at a variety of intensity levels during the last week (Booth, 2000). Higher scores represent greater total metabolic-equivalent-of-task minutes of physical activity per week.

Context sensitivity (assessed at Time 1 and Time 2). The Context Sensitivity Index is a self-report scale that measures participants' ability to identify information about stressful situations that may be helpful for flexibly regulating unpleasant feelings of distress (Bonanno, Maccallum, Malgaroli, & Hou, 2018). In particular, the cue presence score reflects the sensitivity to the presence of meaningful contextual cues. This cue presence score is calculated as the sum of 10 relevant items from the scale. Greater cue presence scores indicate greater context sensitivity (cue presence score range: 10–77).

Intervention acceptability, usability, and treatment fidelity. We will assess the acceptability of the CBMT via questions in the exit interview questionnaire at the study's conclusion. One item assesses feelings associated with the intervention using a Likert scale ranging from 1 (*very unpleasant*) to 5 (*very pleasant*): "In general, how would you describe the feelings you experienced while completing the tablet tasks?" A second item asks about the usability of intervention instructions using a Likert scale ranging from 1 (*very difficult*) to 5 (*very easy*): "How easy or difficult was it for you to understand the instructions for the tablet tasks?" Finally, an open-ended question is asked: "If there is anything you would like to share with the INFORM team, please comment on your experience with completing the tablet tasks, using the eCAP device, or any other aspect of this study." The proportion of all eligible participants who choose to enroll in the intervention study will be assessed to determine whether the patient population is generally open to doing this kind of intervention study. Intervention treatment fidelity will be indexed by the mean proportion of tablet sessions completed.

Other Measures

Demographic information (e.g., age, sex, race, ethnicity, education) is collected by patient interview. Baseline clinical characteristics (e.g., cardiac risk score, Charlson comorbidity index) and relevant psychological characteristics are also collected: baseline PTSD symptoms due to non-ACS trauma (PTSD Checklist-Civilian; Weathers, Litz, Herman, Huska, & Keane, 1993), ACS-induced PTSD symptoms (PTSD Checklist-Specific; Weathers, Litz, Herman, Huska, & Keane, 1994), and depressive symptoms (Patient Health Questionnaire; Kroenke et al., 2009). At Time 1, self-reported reasons for medication nonadherence are collected (e.g., out of routine, feeling down or upset; Voils et al., 2012).

Statistical Analyses

For Aim 1, univariate analysis of variance (ANOVA) tests will test the effect of group on the Time-1-to-2 change in FoR and future time perspective total scores. For Aim 2, zero-order correlation tests will evaluate the associations between each of the two investigated mechanisms (FoR total score and future time perspective total score) at Time 1 and each of the health behavior measures (eCAP proportion of days adherent to heart medication across the entire study monitoring period, Time-2 self-reported medication adherence total score, Time 1 to 2 change in self-reported physical activity total score). For Aim 3, three separate univariate ANOVA models will test the effects of group on each of the three health behavior measures above. Six separate mediation models using linear regression with bootstrapping will test the

indirect effects involving Time 1 to 2 changes in each of the two investigated mechanisms (FoR total score, future time perspective total score) in the associations between group and each of the three health behavior measures above. The plan is for all data analyses to occur after completion of data collection after the breaking of the blind (i.e., no interim data analyses are planned).

Sample Size Estimation

In prior research using a similar intervention in cancer patients ($N_{Analyzed} = 75$), a moderate effect size (Hedges' $g = 0.54$) was found for differences in FoR between the intervention ($n_{Analyzed} = 49$) and sham control ($n_{Analyzed} = 26$) Groups 3 months after the intervention (Lichtenthal et al., 2017). It was determined with G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009) that a sample size of $N = 100$ (50 intervention, 50 control) would be sufficient to achieve 90% power to change FoR in a fixed-effects one-way ANOVA, provided that the effect size was relatively stronger at $f \geq 0.35$ (i.e., Cohen's $d \geq 0.70$), given $\alpha = .05$ and an intention-to-treat design in which missing data due to attrition will be handled with multiple imputation. That sample size with a more lenient specification of 80% power would allow for detection of an effect size of $f = 0.28$ (i.e., Cohen's $d = 0.56$), an effect size closer to that observed by Lichtenthal et al. (2017). Therefore, the target enrollment was set to $N = 100$ to balance the likelihood of detecting a plausible effect, if one exists, with the feasibility of recruiting a sufficient number of patients from the parent study. Results will need to be interpreted cautiously since the study is underpowered to detect smaller, yet still clinically meaningful effects.

Data Management Plan

To protect confidentiality, all collected paper data are stored in a locked filing cabinet in a locked office, and all electronic data are stored on a password-protected server. Any documents linking protected health information with identifiable information are secured with an additional password known only to study staff. Self-reported information is double-entered. Medication adherence is computed using SAS scripting procedures with range checks for date values.

Ethics and Dissemination

The protocol and all study documents have been approved by the institutional review board at CUIMC (IRB-AAAR9458). This committee deemed the active intervention and control procedures to present minimal risk to study participants. No data safety monitoring board was required because the study was deemed by the institutional review board (IRB) to involve minimal risk. All adverse events associated with the study will be monitored by study coordinators and reported promptly to the IRB. The study involves neither planned compensation for harm during the trial nor planned care for participants beyond the trial duration.

This project is conducted with an emphasis on scientific transparency. The first reason for this emphasis concerns the replication crisis in psychological science (Munafò et al., 2017), and the second reason concerns the particular importance of prespecifying targeted mechanisms of behavior change for the mission of the NIH's Science of Behavior Change initiative to conduct open as well as rigorous mechanistic science (Sumner et al., 2018). This project presents an opportunity to capture the measurement and attempted manipulation of FoR in the ACS population in a context of open science. As required by the Department of Health and Human Services in line with the current definition of clinical trials, this trial was preregistered on ClinicalTrials.gov (ID: NCT03853213). In addition, we chose to preregister the trial on the Open Science Framework (OSF; https://osf.io/k7g8c/) in line with prior and ongoing SOBC projects having their hypotheses and results registered there. OSF is a broader platform that allows for the posting of easily navigable measures (all INFORM measures can be found in *Files*/*Measures* at https://osf.io/k7g8c/) as well as the specification of exploratory analyses in addition to the preregistered analyses. The informed-consent forms in English and Spanish are also available on the OSF page. At the conclusion of the study, we plan to make the de-identified study data and the associated processing syntax available on the OSF page. Any relevant changes to the INFORM protocol are updated on the two registration sites and are submitted for approval to the IRB. Trial results will be shared publically via scientific conference presentations, the annual SOBC steering committee meeting, and the SOBC website. Journal publications resulting from this trial will be posted on the study's OSF page to ensure open access for all articles related to this project. All INFORM investigators and study staff are eligible authors for dissemination of trial results.

Discussion

This study will be the first to test whether tablet-based cognitive-affective training tasks are efficacious in reducing fear of future cardiac events in patients with suspected ACS. The study will inform future medication adherence interventions in several ways. First, it will explore whether reducing FoR through CBMT mediates improvements in adherence behavior, and thus will help elucidate whether FoR is an important target for behavior change interventions after ACS. Second, if the study proves to be efficacious in reducing FoR, increasing future time perspective, or improving adherence, it may also serve as a pilot study for a larger trial statistically powered to improve health behaviors in ACS survivors.

The present study has several strengths. First, the double-blinding nature of the study increases its internal validity. Second, the control condition is well matched to the intervention in that they have identical task durations, linguistic stimuli, and instructions. They differ only in the trained locus of attention (cognitive bias modification for attention task) and in the trained interpretation (cognitive bias modification for interpretation task) that are manipulated via the task specifications and feedback. Thus, because of these strengths, any observed group differences after the intervention are likely to be driven by altered patterns of threat-related cognition about ACS. Third, this study is the first to measure FoR and future time perspective in patients with suspected ACS in the weeks following the potentially distressing medical event.

The study has several limitations. First, enrolled patients differ in their cardiovascular medications. The study includes participants with different medication regimen instructions (e.g., one time a day, two times a day) and differing kinds of concerns about side effects that could influence adherence (e.g., dizziness, eczema, gastrointestinal bleeding, tightness in chest). As a related

point, measuring adherence to a single medication may not be representative of patients' global adherence. Second, physical activity measured through self-report may overestimate actual physical activity. Nevertheless, if group differences are observed, they are likely to be meaningful. Third, FoR has not previously been adapted to ACS. However, we will test the validity and reliability of the adapted measure. Fourth, despite the strength of the diverse patient sample, the findings may not generalize to other patient populations due to the single site of a large, busy hospital in upper Manhattan.

These limitations notwithstanding, the INFORM trial takes a critical step toward understanding the role of FoR as a potentially detrimental influence on health behaviors and as a first attempt to modify this putative mechanism in this population. It will exemplify the SOBC experimental medicine approach to behavioral intervention development. Exceedingly few trials addressing medication nonadherence have been mechanistically focused (for a systematic review, see Edmondson et al., 2018). In contrast, the INFORM study attempts to test identified targets (i.e., FoR, future time perspective) as potentially powerful mechanisms of behavior change for further intervention development.

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Received September 6, 2019
Revision received December 17, 2019
Accepted December 20, 2019 ■