



# Longer term benefits of exercise and escitalopram in the treatment of anxiety in patients with coronary heart disease: Six month follow-up of the UNWIND randomized clinical trial

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**Background** Anxiety is a common comorbidity in patients with coronary heart disease (CHD) and is associated with worse prognosis. However, effective treatment for anxiety in CHD patients is uncertain. The UNWIND randomized clinical trial showed that 12-week treatment of escitalopram was better than exercise training or placebo in reducing anxiety in anxious CHD patients. The longer-term benefits of treatment for anxiety are not known.

**Methods** Patients were randomized to 12 weeks of Escitalopram (up to 20 mg), Exercise (3 times/wk), or placebo pill. At the conclusion of treatment, participants were followed for 6-months to determine the persistence of benefit on the primary anxiety endpoint assessed by the Hospital Anxiety and Depression Scale-Anxiety scale (HADS-A) and to assess the effects of treatment on major adverse cardiac events over a follow-up period of up to 6 years.

**Results** Of the 128 participants initially randomized, 120 (94%) were available for follow-up. Participants randomized to the Escitalopram condition exhibited lower HADS-A scores (3.9 [3.1, 4.7]) compared to those randomized to Exercise (5.5 [4.6, 6.3]) ( $P=.007$ ) and Placebo (5.3 [4.1, 6.5]) ( $P=.053$ ). Over a median follow-up of 3.2 years (IQR: 2.3, 4.5), there were 29 adverse events but no significant between-group differences.

**Conclusion** In the UNWIND trial, 12 weeks of escitalopram treatment was effective in reducing anxiety. These beneficial effects were sustained for 6 months posttreatment. Although moderate or vigorous physical activity has a number of health benefits, exercise was not an effective treatment for anxiety in patients with CHD. (*Am Heart J* 2022;251:91–100.)

**Keywords:** Anxiety; Escitalopram; Depression; Exercise

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**Non-standard Abbreviations:** BDI-II, Beck Depression Inventory-II; DSM-5, Diagnostic and Statistical Manual-5th edition; GAD-7, Generalized Anxiety Disorder 7-item questionnaire; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; MDD, Major Depressive Disorder; PSS, Perceived Stress Scale; 6MWT, Six Minute Walk Test; SSRI, Selective Serotonin Reuptake Inhibitor; STAI-T, Spielberger State-Trait Inventory-Trait; UNWIND, Understanding the Benefits of Exercise and Escitalopram in Anxious Patients With Coronary Heart Disease.

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Coronary heart disease (CHD) is the leading cause of death in the United States; more than 600,000 Americans suffer a fatal cardiac event each year.<sup>1</sup> In addition to such traditional risk factors as hypertension and hyperlipidemia, psychosocial factors also are associated with increased adverse health outcomes in patients with CHD.<sup>2-4</sup> In particular, major depressive disorder (MDD) and elevated depressive symptoms are predictors of increased mortality and morbidity in patients with CHD.<sup>5-7</sup> As a result, the American Heart Association has recommended that clinicians assess depression in patients with CHD, and refer for treatment as needed.<sup>8</sup>

More recently, the importance of anxiety as a risk factor has received growing recognition,<sup>9,10</sup> particularly since anxiety disorders are as prevalent as depression in the general population<sup>11,12</sup> as well as in cardiac popula-

tions, with estimates ranging from 25% to 44%.<sup>13-15</sup> There also is mounting evidence that anxiety may be an independent predictor of adverse events in healthy adults and in patients with CHD.<sup>16-24</sup>

While the clinical significance of depression and anxiety is widely recognized, effective treatment in patients with CHD has remained elusive. Selective serotonin reuptake inhibitors (SSRIs) have been evaluated for the treatment of clinical depression, but with mixed results.<sup>25-28</sup> Despite the prevalence and potential prognostic significance of anxiety in CHD populations, there have been few randomized clinical trials (RCTs) targeting anxious CHD patients. Although SSRIs are effective in treating anxiety in the general population,<sup>29,30</sup> few studies have examined the efficacy of SSRIs for treating anxiety specifically in CHD patients. Exercise also has been considered as a potential treatment for depression and anxiety. Indeed, a number of studies have shown that exercise improves depression,<sup>31,32</sup> including depression in patients with CHD.<sup>33</sup> However, to our knowledge, the UNWIND study remains the only RCT that examined and compared the effects of exercise, as well as the SSRI escitalopram, on anxiety in patients with CHD.<sup>34</sup> We previously reported that escitalopram, and to a lesser extent exercise, reduced anxiety compared to placebo controls immediately following 12 weeks of treatment.<sup>35</sup> The present report considers the extent to which anxiety reduction benefits persisted 6-months following completion of the UNWIND interventions, and also examines posttreatment clinical outcomes over a follow-up of up to 6 years.

## Methods

### Trial overview

UNWIND was a single-site, parallel group RCT designed to evaluate the effects of aerobic exercise, escitalopram, or placebo pill on anxiety symptoms and CHD biomarkers among anxious individuals with CHD. Enrollment began in January 2016 and the interventions were completed in May 2020. After completing the 12-week intervention, participants were given the opportunity to continue with their assigned treatment, switch to the alternative treatment (ie, exercise or escitalopram), receive other treatments (eg, other psychotropic medications or psychotherapy), or discontinue treatment entirely. Patients were subsequently followed annually for clinical events through December 2021. The trial was approved by the institutional review board at Duke University Medical Center, and written informed consent was obtained from all participants. Follow-up assessments were performed 6-months after completion of the interventions; the last 6-month, posttreatment assessment was performed in December 2020. The study is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ID: NCT02516332). The immediate effects of the interventions on anxiety and other end-

points have been reported previously;<sup>35</sup> the results of the 6-month posttreatment assessments are described in this manuscript.

### Participants

One hundred twenty-eight men and women with CHD and an anxiety symptom severity score of  $\geq 8$  on the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A)<sup>36</sup> and/or a DSM-5 primary diagnosis of an anxiety disorder were enrolled in the trial. Exclusion criteria included a primary psychiatric diagnosis other than an anxiety disorder, current treatment for a psychiatric disorder, or participation in any regular exercise  $> 1$  d/wk.

### Treatment conditions

#### Aerobic exercise

Participants exercised 3 times per week for 45 minutes per session under supervision at a local state-certified cardiac rehabilitation facility in the Research Triangle area of North Carolina (in Durham, Chapel Hill, Burlington, or Raleigh, NC). Each exercise session consisted of 10 minutes of warm-up exercises followed by 35 minutes of continuous walking, biking, or jogging at 70%-85% of heart rate reserve.

#### Escitalopram and/or Placebo pill

Participants were started on 5 mg once per day of either escitalopram or placebo. Daily doses were titrated to 10 mg at week 2 and 15 mg or placebo equivalent at week 3 if there was no change or only minimal improvement in anxiety. At week 4, if there was no change or only minimal improvement in anxiety, and no or minimal side effects, a maximum daily dose of 20 mg or placebo equivalent was prescribed. Participants met with the treating psychiatrist at weeks 1, 2, 4, 8, and 12.

### Six-month follow-up assessments

Six months after completing the intervention, participants were surveyed for any postintervention psychiatric treatments and current exercise habits; participants also completed a 6-minute walk test (6MWT) to assess functional capacity<sup>37</sup> and a battery of psychometric questionnaires to assess anxiety as well as secondary measures of psychosocial functioning including depression and emotional distress.

#### Physical activity and functional capacity

Physical activity was quantified by the Godin Leisure Time Exercise Questionnaire.<sup>38,39</sup> Functional capacity was assessed by measuring the distance walked on the Six Minute Walk Test (6MWT).<sup>37</sup> The 6MWT is a self-paced, timed test to determine the total distance that a patient is able to walk in 6 minutes.

#### Anxiety

The primary endpoint was the score on the 14-item Hospital Anxiety and Depression Scale (HADS).<sup>36</sup> Secondary anxiety assessments included the Spielberger

State-Trait Anxiety Inventory-Trait (STAI),<sup>40</sup> the Generalized Anxiety Disorder 7-item questionnaire (GAD-7),<sup>41</sup> and the 14-item Hamilton Anxiety Rating Scale (HAMA).<sup>42</sup>

### Depression

Depressive symptoms were assessed by the Beck Depression Inventory-II (BDI-II)<sup>43</sup> and the HADS-D.<sup>36</sup>

### General distress

General distress was measured by the General Health Questionnaire (GHQ),<sup>44</sup> a 14-item screening questionnaire for nonpsychotic psychiatric disorders.

### Perceived stress

Perceived stress was measured by the Perceived Stress Scale (PSS),<sup>45</sup> a 10-item survey that taps the degree to which individuals feel that events in their lives are unpredictable and uncontrollable.

### Clinical outcomes

In order to document clinical events, medical records were reviewed by a physician's assistant, blinded to treatment condition, and events were categorized based on ACC and/or AHA criteria,<sup>46</sup> including all-cause mortality, fatal and nonfatal myocardial infarction, coronary or peripheral artery revascularization, stroke and/or transient ischemic attack, and unstable angina requiring hospitalization.

### Data analysis

Data were analyzed using SAS version 9.4 (Cary, NC). Differences between those lost to follow-up and those participants who were available for 6-month follow-up assessments were compared using chi-square analyses for categorical data and t-tests for continuous variables. For analyses of treatment group differences in psychosocial function at follow-up, repeated measures mixed modeling was used with posttreatment and 6-month follow-up assessments serving as the outcome variables controlling for the pretreatment level of the respective outcome, age, sex, race, history of myocardial infarction, and treatment group as the predictor of interest. Parallel analyses were conducted for HADS-A, our primary endpoint, and the STAI and other ancillary measures of anxiety. We also assessed depression with the HADS-D and the BDI-II. We examined treatment group differences in 6MWT distance at 6-month follow-up in order to characterize participants' functional capacity. In order to delineate planned group contrasts and account for potential differential treatment patterns following posttreatment assessments, we first examined preplanned contrasts and conducted unadjusted follow-up comparisons of individual group differences. For clinical event outcomes, we examined the impact of treatment on major adverse cardiac events (MACE), including a composite of total death, nonfatal myocardial infarction, coronary revascularization, stroke, and hospitalization due to worsening angina. For these analyses, we utilized the Wei-Lin-Weissfeld clustered Cox proportional hazards model approach in order to maxi-

mize power. Two preplanned contrasts were conducted, including a comparison of 1) the 2 active intervention groups (Escitalopram and Exercise) to Placebo and 2) Escitalopram and Exercise. Multiple imputation was used to account for missing data. Assumptions regarding linearity, additivity, and independence were assessed and found to be acceptable prior to analysis.

## Results

Of the 128 participants initially randomized, 120 (94%) were able to provide at least partial assessments at follow-up. Due to COVID-19, 14 patients were unavailable for at least some in-person follow-up assessments; 114 patients (89%) were available for 6-month in-person follow-up evaluations, including 49 participants from the Escitalopram group (98%), 44 from the Exercise group (90%), and 21 from the Placebo group (91%) (Figure 1). As previously reported,<sup>35</sup> groups were comparable on virtually all demographic and clinical characteristics at baseline. The sample was older (mean age = 64.6 years), and 71% were male and 72% white. The sample was considered moderately-severely anxious at baseline based upon an initial Hamilton-Anxiety score of 15.9 (SD = 6.4). Examination of demographic and clinical correlates of participants being lost to follow-up (N = 14) revealed that 2 participant characteristics were associated with differential attrition: the presence of a clinically diagnosed anxiety disorder (15% vs 0%,  $P = .015$ ) and female sex (22% vs 7%,  $P = .014$ ). No other background or clinical characteristics were significantly associated with differential loss to follow-up.

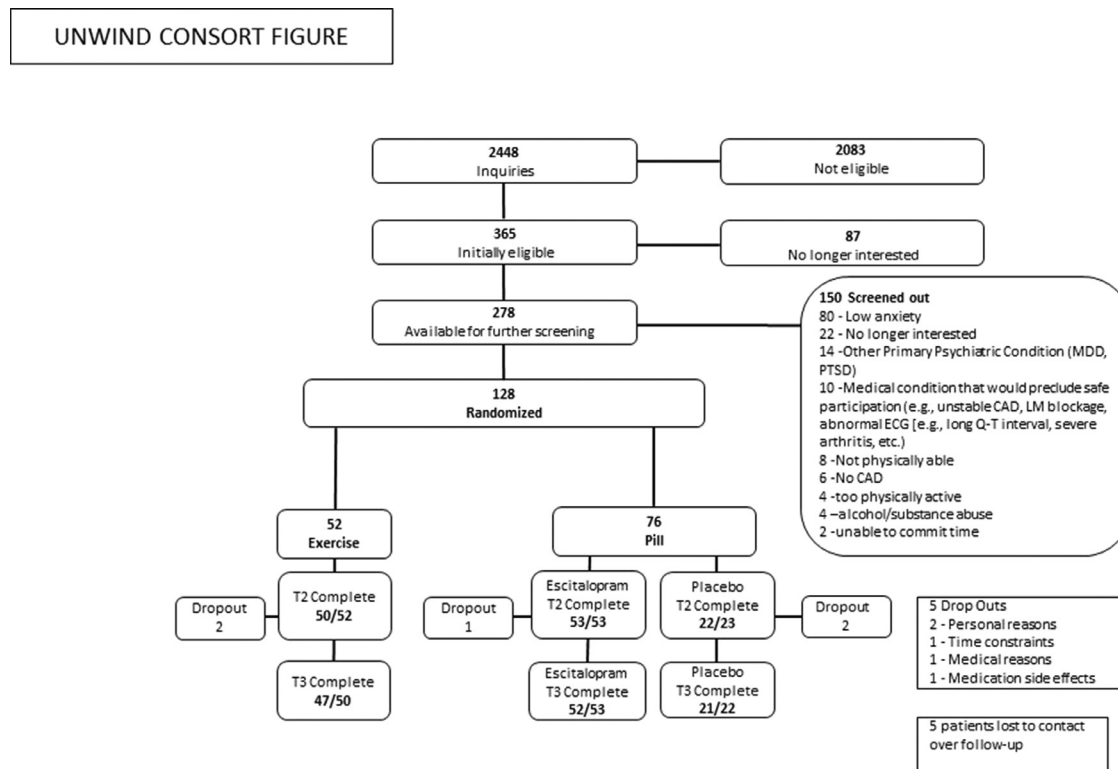
### Treatments received during the six-month follow-up period

Participants were asked to report any psychological treatments that they received during the 6-month postintervention follow-up period, including participation in counseling and/or psychotherapy, anxiolytic medication use, and use of herbal medications with presumed psychotropic properties. A third of participants (n = 41) reported taking psychotropic medications during the follow-up period, including 28 participants in Escitalopram, 11 in Exercise, and 2 in Placebo (chi-square = 25.4,  $P < .001$ ). More than half (N = 27) of the participants randomized to the Escitalopram condition continued to take escitalopram, compared to 3 participants in Exercise and none in Placebo; 2 patients in Exercise and 1 patient in Placebo were placed on benzodiazepines (ie, alprazolam, diazepam, and lorazepam). In addition, 14 participants (11%) reported taking herbal supplements and 7 patients (5%) reported receiving counseling or psychotherapy.

### Physical activity and functional capacity

Self-reported physical activity data were obtained from the Godin Leisure Time Exercise Questionnaire.<sup>38</sup> Participants reported engaging in 2.6 (SD = 2.5) bouts of

Figure 1



moderate-to-vigorous physical activity per week, corresponding to a median of 60 min/wk (IQR: 0, 120), with levels of 90 min/wk in Exercise (IQR: 30, 150), 60 min/wk in Escitalopram (IQR: 0, 120), and 30 min/wk in Placebo (IQR: 0, 120).

Examination of 6MWT distance revealed that participants randomized to Exercise achieved greater distance compared to the other groups. Examination of preplanned contrasts revealed no differences when both treatment groups were compared to Placebo ( $P = .104$ ) and Exercise exhibiting greater 6MW distance compared to Escitalopram ( $P = .009$ ). Treatment group 6MWT distances were 505 meters (479, 530) for Exercise, 457 meters (431, 482) for Escitalopram, and 445 meters (406, 484) for Placebo (see Figure 2).

### Anxiety

Examination of changes in HADS-A scores revealed that the Escitalopram group continued to show reduced anxiety relative to the Exercise and Placebo groups (Table 1). Examination of preplanned contrasts revealed no significant differences between both treatment groups and Placebo ( $P = .340$ ) but a significant dif-

ference between Escitalopram and Exercise ( $P = .007$ ). Follow-up analyses also revealed that the Escitalopram group tended to exhibit lower HADS-A scores compared to Placebo ( $P = .053$ ) (Figure 3, left panel). Patients in the Escitalopram condition who continued to take the medication had lower HADS-A scores (3.7 [2.6,4.8]) compared to those randomized to Escitalopram but who discontinued medication at the end of 12 weeks (4.4 [3.1,5.7]), although even their scores remained lower compared to Exercise (5.5 [4.6,6/3]) and Placebo (5.3 [4.1,6.5]).

Ancillary measures of anxiety also were examined including the STAI, GAD-7 and HAM-A (see Table 1). Results largely paralleled our primary outcomes with a somewhat weaker pattern of group differences. For the STAI, results revealed marginally significant improvements in the STAI in the active treatment groups compared to Placebo ( $P = .053$ ) and nonsignificant differences between the Escitalopram and Exercise groups ( $P = .293$ ). Explanatory follow-up analyses revealed that the Escitalopram group exhibited lower anxiety compared to Placebo ( $P = .033$ ), without significant differences or between Exercise and Placebo ( $P = .195$ ). A similar pattern

**Table I.** Six-month follow-up scores on 4 self-report measures of anxiety.

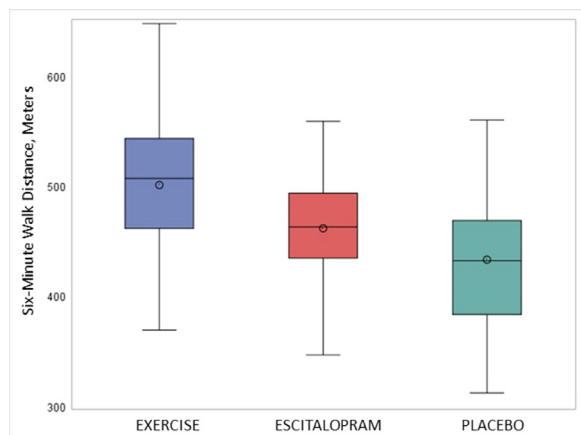
Group	HADS-A	STAI-T	GAD-7	HAM-A
Escitalopram	3.9* (3.1, 4.7)	34.3** (32.7, 36.0)	2.2* (1.2, 3.1)	8.9 (7.4, 10.3)
Exercise	5.5 (4.6, 6.3)	35.6 (33.9, 37.3)	3.7 (2.7, 4.7)	10.6 (9.1, 12.1)
Placebo	5.3 (4.1, 6.5)	37.6 (35.1, 40.1)	3.3 (1.8, 4.8)	9.3 (7.1, 11.5)

Note:

\*  $P < .05$  Escitalopram v Exercise

\*\*  $P < .05$  Escitalopram v Placebo; \*\*  $P < .10$  Escitalopram v Exercise GAD 7 = Generalized Anxiety Disorder 7 items; HADS-A = Hospital Anxiety and Depression Scale-Anxiety subscale; HAM-A = Hamilton Anxiety Scale; STAI-T = Spielberger State-Trait Anxiety Inventory-Trait.

**Figure 2**



Six-minute walk test distance walked at follow-up. Blue = Exercise, Red = Escitalopram, Green = Placebo.

was noted for the GAD-7, but with no significant differences between active treatment groups and Placebo ( $P = .702$ ), but lower anxiety in Escitalopram compared to Exercise ( $P = .032$ ). For the HAM-A, we found no differences between active treatment groups and Placebo ( $P = .822$ ), but a trend for the Escitalopram group to have lower HAM-A scores compared to Exercise ( $P = .088$ ).

### Depression

In addition to anxiety outcomes, we also examined treatment group differences in depressive symptoms as measured by the HADS-D and BDI-II. For both depressive symptom measures, we observed a parallel pattern of findings to the anxiety outcomes, with the Escitalopram group exhibiting the largest improvements. For the HADS-D, we found no differences between active treatment groups and Placebo ( $P = .986$ ) and Escitalopram had marginally lower scores compared with Exercise ( $P = .058$ ). Treatment group scores were 3.1 (2.4, 3.9) for Escitalopram, 4.2 (3.4, 5.0) in Exercise, and 3.7 (2.5, 4.8) in Placebo. For the BDI-II, we found no differences between active treatments and Placebo ( $P = .684$ ), but Escitalopram had lower scores compared with Exercise

**Table II.** MACE events by treatment group.

Event	Escitalopram	Exercise	Placebo
Nonfatal MI	1	2	3
Fatal MI	1	0	0
Revascularization	2	10	1
Stroke	1	1	1
Hospitalization	2	0	1
Total events	7	13	6

( $P = .037$ ). Treatment group BDI-II scores were 5.8 (4.3, 7.3) for Escitalopram, 8.2 (6.6, 9.8) for Exercise, and 7.5 (5.2, 9.9) for Placebo.

### Ancillary psychosocial measures

For the measure of general distress, we found no differences in GHQ scores between active treatments and Placebo ( $P = .467$ ); participants randomized to the Escitalopram condition tended to exhibit lower scores compared with Exercise ( $P = .052$ ). Group scores were 8.6 (7.4, 9.7) in Escitalopram, 10.2 (9.0, 11.3) in Exercise, and 10.1 (8.4, 11.8) in Placebo.

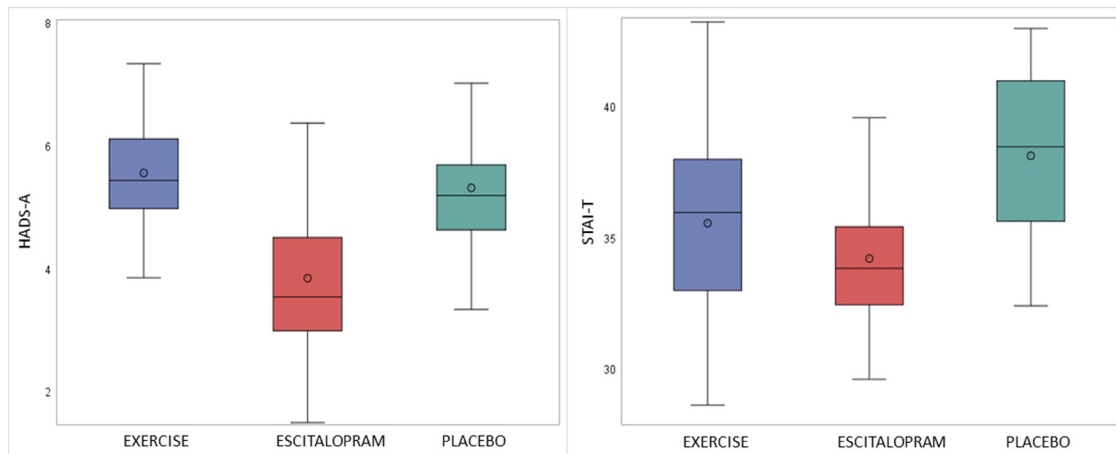
With respect to perceived stress, we found that both active treatment groups reported reduced stress compared to Placebo ( $P = .015$ ) and there were no differences between Escitalopram and Exercise ( $P = .561$ ). Scores on the PSS scale were 18.0 (15.9, 20.0) for Exercise, 17.1 (15.2, 19.1) for Escitalopram, and 21.8 (18.8, 24.9) for the Placebo condition.

### Major adverse cardiac event clinical outcomes

Participants were followed for up to 6 years to record the occurrence of clinical events. Over a median follow-up of 3.2 years (IQR: 2.3, 4.5), 26 participants experienced at least one MACE event including 13 (25%) participants for Exercise, 7 (13%) for Escitalopram, and 6 (27%) for Placebo (Table II). We found no differences between the 2 active treatment groups or Placebo (HR = 1.01 [0.77, 1.32],  $P = .958$ ), nor between Escitalopram and Exercise (HR = 1.16 [0.59, 2.26],  $P = .673$ ).

### Discussion

Results of the UNWIND clinical trial found that escitalopram, but not aerobic exercise, resulted in reduced

**Figure 3**

(left panel). HADS-A scores at Baseline, 12-weeks and 6-month follow-up. Blue = Exercise, Red = Escitalopram, Green = Placebo. There was no difference between Exercise/Escitalopram and Placebo ( $P = .340$ ) but a significant difference between Escitalopram and Exercise ( $P = .007$ ). HADS-A scores also tended to be lower for Escitalopram compared to Placebo ( $P = .053$ ). Figure 3 (right panel). STAI-T scores at Baseline, 12-weeks, and 6-month follow-up. Blue = Exercise, Red = Escitalopram, Green = Placebo. Escitalopram and Exercise tended to have lower trait anxiety compared to Placebo ( $P = .053$ ). There was no difference in STAI-T scores between Escitalopram and Exercise ( $P = .293$ ), but the Escitalopram group exhibited less trait anxiety compared to Placebo ( $P = .033$ ). The difference in STAI-T scores between Exercise and Placebo was not significant ( $P = .195$ ).

anxiety relative to placebo controls after 12 weeks. This 6-month follow-up of UNWIND participants revealed persistent benefit for patients who received escitalopram. After 6 months, participants randomized initially to escitalopram reported consistently lower scores on 3 separate self-report measures (ie, the HADS-A, STAI-T, and GAD-7) compared to those who underwent exercise or who received a placebo pill. Moreover, patients who received escitalopram also had lower scores on measures of depression and reported less distress. Interestingly, those participants who were randomized to the exercise intervention achieved greater 6-minute walk distances at follow-up, and reported having engaged in more moderate-high intensity exercise relative to those participants who received either escitalopram or placebo. However, contrary to previous studies demonstrating the antidepressant effects of exercise,<sup>31</sup> higher levels of physical activity and better functional capacity among those participants randomized to Exercise did not translate into greater improvements in anxiety and depression relative to placebo controls. This apparent lack of benefit in depression is consistent with findings that comorbid anxiety may attenuate the beneficial effects of exercise on depression.<sup>47</sup>

Because depression and anxiety in CHD patients have been shown prospectively to be associated with increased mortality and greater risk for untoward cardiac events,<sup>5-7,48</sup> there are compelling reasons for treating depression and anxiety in this patient population. However,

most attention has focused on the need to assess and treat depression rather than anxiety. Several studies, including the ENRICH trial, have examined the effects of treating depressed post-MI patients using cognitive behavior therapy<sup>49</sup> and several pharmacologic RCTs have examined the effects of selective serotonin reuptake inhibitors (SSRIs) on depressive symptoms and outcomes in cardiac patients.<sup>25-27, 50, 51</sup> For example, the SADHART study<sup>26</sup> found no differences between patients receiving sertraline compared to placebo, but reported greater reductions in depressive symptoms in the subset of patients with more severe depression. A subsequent trial, SADHART-CHE,<sup>25</sup> found no advantage for sertraline over placebo in either reducing depression or in improving clinical outcomes.

Escitalopram has been shown to be effective in reducing anxiety and depression in the general population<sup>52</sup> but in cardiac patients escitalopram has produced mixed results. In the MOOD-HF trial,<sup>53</sup> escitalopram compared with placebo did not significantly reduce all-cause mortality or hospitalization, and there was no significant improvement in depression in patients with heart failure. Similarly, in the REMIT study of patients with mental stress-induced myocardial ischemia,<sup>51</sup> there were no group differences between those patients receiving 6 weeks of escitalopram and those receiving placebo on measures of depression, trait anxiety and perceived stress. In contrast, escitalopram was found to be safe and effective in preventing depression in a sam-

ple of nondepressed Danish patients with acute coronary syndrome.<sup>54,55</sup> The Escitalopram for Depression in Acute Coronary Syndrome (EsDEPACS) trial found that 24-weeks of treatment with escitalopram was effective in reducing depressive symptoms and in lowering the risk of major adverse events compared to placebo controls.<sup>56</sup> Moreover, in a secondary analysis of the EsDPACS trial, escitalopram also was shown to reduce anxiety symptoms relative to placebo, although 27% of the original sample was lost to follow up and were not included in the analyses.<sup>57</sup>

In the present study, escitalopram was found to be a safe and effective anxiolytic treatment for CHD patients with high anxiety. Unlike previous studies that targeted CHD patients with major depression, the UNWIND trial targeted patients with anxiety, specifically excluding patients with a primary diagnosis of depression. Almost three-fourths of the sample had a diagnosed anxiety disorder, and baseline scores on the HADS-A were in the moderate-severe range. Escitalopram produced clinically meaningful reductions in anxiety, as well as significant reductions in depression, which persisted for 6 months. In contrast, exercise produced relatively little psychological benefit. Participants randomized to the exercise intervention had similar levels of depression and anxiety to those receiving placebo after 6 months, despite being more likely to engage in physical activity and achieving greater functional capacity. RCTs examining the effects of exercise on anxiety have produced disparate results, in part because participants without elevated anxiety or with no anxiety diagnosis were included in these studies. For example, in a meta-analysis of studies that included healthy participant without elevated anxiety, Conn<sup>58</sup> found significant heterogeneity in study designs and outcomes. Bartley and colleagues<sup>59</sup> examined 7 exercise RCTs in 407 individuals with any diagnosed anxiety disorder and reported no significant difference between exercise and control conditions for anxiety outcomes. Furthermore, few studies have targeted anxious CHD patients, and to our knowledge UNWIND is the only RCT that has specifically used exercise to treat anxiety. In a study of patients enrolled in cardiac rehabilitation, Lavie and Milani<sup>13</sup> reported more than a 69% reduction in anxiety among highly anxious participants; however, this was not a RCT, there was no control group, and exercise was only 1 component of the multicomponent intervention. Stonerock and colleagues<sup>60</sup> reviewed 12 randomized trials in which participants with a diagnosis of an anxiety disorder or elevated symptoms of anxiety were randomly assigned to exercise as one of the treatment arms of the trial. Most studies were considered to suffer from significant methodological limitations that left the issue of exercise to treat anxiety unresolved. Results of the UNWIND study, which targeted anxious CHD patients, are consistent with these conclusions and suggest that despite the benefits of exercise for improving functional

capacity and reducing CHD risk, it should not be recommended as a treatment for anxiety.

**Limitations.** Although 94% of patients enrolled in the UNWIND trial were available for follow-up, the sample was small and there were few MACE events, despite the follow-up interval of up to 6 years. Therefore, the longer-term benefits of treating anxiety on clinical outcomes will require further study. More than half of the participants randomized to escitalopram continued with the medication over the 6-month follow-up, while 11 participants in Exercise and 2 participants in Placebo received anxiolytic medications during the follow-up period. Differences in treatments received during the follow-up period may have contributed to differential anxiety outcomes for the respective treatment groups. Although the participants in the Escitalopram condition had almost 50% fewer MACE outcomes compared to Exercise and Placebo, this difference was not statistically significant because the study was underpowered to detect group differences in clinical events.

**Conclusions.** Escitalopram is an effective treatment for anxiety in patients with CHD. In the UNWIND trial, 12 weeks of treatment was effective in reducing anxiety, as well as depression and general distress. Moreover, these beneficial effects appeared to persist for 6 months post-treatment, especially for those who continued treatment. While patients randomized to the Exercise condition had greater functional capacity at 6-month follow-up, and less perceived stress compared to placebo controls, exercise was not effective in reducing symptoms of anxiety and depression. Although exercise has a number of health benefits, it should not be considered an effective treatment for anxiety in patients with CHD.

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## CRedit authorship contribution statement

**James A. Blumenthal:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing - original draft. **Patrick J. Smith:** Writing - review & editing, Software, Formal analysis, Validation, Visualization, Writing - original draft. **Wei Jiang:** Investigation, Writing - review & editing. **Alan Hinderliter:** Funding acquisition, Investigation, Methodology, Resources, Writing - review & editing. **Lana L. Watkins:** Investigation, Writing - review & editing. **Benson M. Hoffman:** Investigation, Writing - review & editing. **William E. Kraus:** Investigation, Writing - review & editing. **Stephanie Mabe:** Visualization, Validation, Data curation, Writing - review & edit-

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James Blumenthal and Patrick Smith had full access to all data and take responsibility for the integrity of the data and for the accuracy of the data analysis.

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