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Yoga-Based Cardiac Rehabilitation After Acute Myocardial Infarction

A Randomized Trial

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ABSTRACT

BACKGROUND Given the shortage of cardiac rehabilitation (CR) programs in India and poor uptake worldwide, there is an urgent need to find alternative models of CR that are inexpensive and may offer choice to subgroups with poor uptake (e.g., women and elderly).

OBJECTIVES This study sought to evaluate the effects of yoga-based CR (Yoga-CaRe) on major cardiovascular events and self-rated health in a multicenter randomized controlled trial.

METHODS The trial was conducted in 24 medical centers across India. This study recruited 3,959 patients with acute myocardial infarction with a median and minimum follow-up of 22 and 6 months. Patients were individually randomized to receive either a Yoga-CaRe program (n = 1,970) or enhanced standard care involving educational advice (n = 1,989). The co-primary outcomes were: 1) first occurrence of major adverse cardiovascular events (MACE) (composite of all-cause mortality, myocardial infarction, stroke, or emergency cardiovascular hospitalization); and 2) self-rated health on the European Quality of Life–5 Dimensions–5 Level visual analogue scale at 12 weeks.

RESULTS MACE occurred in 131 (6.7%) patients in the Yoga-CaRe group and 146 (7.4%) patients in the enhanced standard care group (hazard ratio with Yoga-CaRe: 0.90; 95% confidence interval [CI]: 0.71 to 1.15; p = 0.41). Self-rated health was 77 in Yoga-CaRe and 75.7 in the enhanced standard care group (baseline-adjusted mean difference in favor of Yoga-CaRe: 1.5; 95% CI: 0.5 to 2.5; p = 0.002). The Yoga-CaRe group had greater return to pre-infarct activities, but there was no difference in tobacco cessation or medication adherence between the treatment groups (secondary outcomes).

CONCLUSIONS Yoga-CaRe improved self-rated health and return to pre-infarct activities after acute myocardial infarction, but the trial lacked statistical power to show a difference in MACE. Yoga-CaRe may be an option when conventional CR is unavailable or unacceptable to individuals. (A study on effectiveness of YOGA based cardiac rehabilitation programme in India and United Kingdom; CTRI/2012/02/002408). (J Am Coll Cardiol 2020;75:1551–61) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

EQ-5D-5L = European Quality of Life–5 Dimensions–5 Level

Yoga-CaRe = yoga-based cardiac rehabilitation

Cardiac rehabilitation is an established standard of care after acute myocardial infarction with Class I recommendation for use by the European Society of Cardiology, American Heart Association, and American College of Cardiology guidelines (1,2). It is a complex intervention involving multidisciplinary teams to deliver exercise training, stress management, psychosocial support, and secondary prevention (1,2). Cardiac rehabilitation programs have been shown to improve functioning, quality of life, and cardiovascular morbidity (3); yet, participation in cardiac rehabilitation programs remains highly variable worldwide (4,5). The infrastructure and multidisciplinary teams needed to deliver such programs are expensive and lacking in low- and middle-income countries, such as India (6,7). In many high-income countries, such as the United States and United Kingdom, participation in cardiac rehabilitation programs is low among some subgroups (e.g., elderly, women, low-income) (4,5). Potentially, low-cost models of cardiac rehabilitation based on traditional mind-body practices (e.g., yoga, tai chi), could improve availability of cardiac rehabilitation in low- to middle-income countries and also increase options of exercise training in high-income countries (8–10). Despite the widespread interest and ad hoc addition of such practices to conventional cardiac rehabilitation programs, the effectiveness and safety of cardiac rehabilitation programs based on traditional mind-body practices has not been robustly evaluated.

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Yoga is a traditional Indian mind-body practice that has gained worldwide popularity. It combines gentle physical exercises (physical functioning) with breathing and meditation (psychological functioning), and promotes healthy lifestyles (secondary prevention), thereby inherently addressing the key objectives of cardiac rehabilitation (11). A few small-scale trials have evaluated the benefits of yoga-based cardiac rehabilitation programs (i.e., multicomponent interventions, including yoga as one of the components) in patients with coronary artery disease and found improvements in functioning, quality of life, cardiovascular risk factors, and risk of recurrent cardiac events (12–14). We systematically developed a cardiac rehabilitation program based on yoga (Yoga-CaRe) and evaluated its clinical effectiveness and safety in a large randomized trial in India.

METHODS

TRIAL DESIGN AND OVERSIGHT. The study protocol is published (15). The trial was conducted using a PROBE (Prospective Randomized Open, Blinded-Endpoint) design. The protocol was approved by the institutional review boards of the Centre for Chronic Disease Control, New Delhi, India; London School of Hygiene & Tropical Medicine, United Kingdom; and the participating centers. Written informed consent was obtained from all the participants. The trial was sponsored by the Indian Council of Medical Research and the Medical Research Council, United Kingdom, who had no role in the conduct or reporting of the trial.

All trial functions, including randomization, data collection and management, site monitoring, endpoint adjudication, and statistical support, were performed at the Centre for Chronic Disease Control. An independent data and safety monitoring committee checked the safety and efficacy data.

TRIAL POPULATION. The trial was conducted in 24 centers across India. Patients aged 18 to 80 years, with acute myocardial infarction within the past 14 days were eligible if they were willing and able to complete the hospital-based cardiac rehabilitation program. Acute myocardial infarction was confirmed by the World Health Organization's definition (presence of symptoms of ischemia and changes in electrocardiogram) or the Third Universal Definition of Myocardial Infarction (elevation of a cardiac biomarker along with the presence of either symptoms of myocardial infarction or changes in electrocardiogram) (16). Patients were excluded if they practiced yoga regularly (i.e., >3 h per week) or were participating in other clinical trials, as were those with diseases that limited their life span to <1 year or were considered unlikely to complete the study by the local investigator. Patients provided written informed consent before being randomly

†The Yoga-CaRe trial investigators are listed in the Supplemental Appendix. This research was supported by the Indian Council for Medical Research, India (ICMR-58/1/9/MRC-ICMR/2009/NCD-II) and Medical Research Council, United Kingdom (MRC-MR/J000175/1). Dr. Chathurvedi has served as a member of the Data Safety and Monitoring Committee for AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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assigned, in a 1:1 ratio, to receive either Yoga-CaRe or enhanced standard care. Block randomization, stratified by centers, age (<60 or ≥60 years), and sex, was carried out by a central computer program using an interactive Web response system.

INTERVENTIONS. The details and development process of the Yoga-CaRe program is published (17). Briefly, the Yoga-CaRe program was developed through a structured process, involving literature (scientific and yoga) reviews and consultations with experts (e.g., yoga, cardiac rehabilitation) to identify the most suitable (safe and effective) yoga exercises for each component of a conventional cardiac rehabilitation program. The draft program was extensively reviewed with yoga and cardiac rehabilitation experts, piloted, and iteratively refined before it was finalized.

The Yoga-CaRe program involved 13 direct contact sessions spread over 12 weeks, with the first session delivered within 2 weeks of the index cardiac event. The first 2 sessions were delivered individually and the remainder in groups at the hospital. Group sessions typically lasted for approximately 75 min and involved a set of gentle yoga exercises, including breath control, meditation and relaxation exercises, followed by a discussion on lifestyle and psychosocial concerns (Supplemental Tables 1 to 3). The program allowed for variable combinations and personalization of exercises to accommodate varying levels of fitness of the patients. The sessions were led by yoga teachers who were trained in the delivery of the Yoga-CaRe program. The intervention was standardized with the help of a training video and manual and annual retraining sessions. Intervention fidelity was ensured through appropriate feedback following regular on-site visits and video recording of a random subset of Yoga-CaRe sessions. The patients were given an instruction booklet and video in the local language and encouraged to practice the recommended yoga exercises at home.

Patients in the enhanced standard care arm received 3 sessions of educational advice with the help of a leaflet, spread over the same time period as the Yoga-CaRe sessions. The educational advice was provided by a different member of the study team (i.e., not the yoga teacher) to avoid "contamination" of the treatment arms. Both groups of patients received the same medical care available to patients at the hospital. As is typical of India, most centers (n = 19) did not offer any form of cardiac rehabilitation.

TRIAL OUTCOMES. The trial had 2 primary outcomes: occurrence of a major adverse cardiovascular event during follow-up and self-rated health at 12 weeks. A major adverse cardiovascular event was a composite of death from any cause, nonfatal myocardial infarction, nonfatal stroke, or emergency cardiovascular hospitalization. Events were adjudicated by an independent committee unaware of trial-group assignments, using standard definitions specified in the protocol. Self-rated health was assessed by the visual analogue scale of the European Quality of Life (EQ-5D-5L) questionnaire, which was completed at baseline and at 12 weeks (18). We pre-specified visual analogue scale as the primary outcome because the descriptive component of EQ-5D-5L lacks conversion into utilities for India.

The pre-specified secondary endpoints were return to pre-infarct activities, tobacco cessation, and medication adherence at 12 weeks. Return to pre-infarct activities was assessed by the Reintegration to Normal Living Index questionnaire (score range from 0 to 110, higher score indicates greater integration) (19). Adherence to prescribed medication was assessed by questions derived from a standard instrument (20). Tobacco cessation was assessed by self-reports of tobacco use at baseline and at 12 weeks by a standard questionnaire. Safety data were collected on serious adverse events, namely noncardiac hospitalizations during the trial and any adverse event during the Yoga-CaRe sessions.

Additional endpoints analyzed were individual components of the adverse major cardiac events, and the descriptive component of the EQ-5D-5L (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

Trial outcome data were collected every 3 months during routine clinical visits. Those missing their clinic appointments were followed up by a telephone call. Participants were followed until the end of the trial, with a pre-specified minimum follow-up period of 6 months (Supplemental Table 4).

STATISTICAL ANALYSIS. We needed to enroll 3,102 patients to give the trial 80% power (at 0.05 significance level) to detect a 20% reduction in event rates between the treatment groups, assuming an overall adverse cardiovascular event rate of 20% (anticipated from the national registry data), allowing for 10% loss to follow-up (21). Under similar assumptions, 808 patients were needed to detect a 5% difference in self-rated health on the visual analogue scale of the EQ-5D-5L. A lower than anticipated number of events (all-cause mortality, myocardial infarction, or stroke) mid-trial (December 2016) prompted the inclusion of emergency cardiovascular hospitalization to the major adverse cardiovascular event outcome. As

further increase in sample size was not possible, the data and safety monitoring committee recommended cessation of enrollment at 4,000 patients and continued follow-up after reporting the preliminary results, which we present here.

Primary analyses were performed on all participants according to the intention-to-treat principle. Cardiovascular event rates were estimated by the Kaplan-Meier method. Follow-up of the patients was censored on September 30, 2018, or at the last known event-free time point, whichever came first. The hazard ratios for first occurrence of a major adverse cardiovascular event were determined using a Cox proportional hazards model, and the Kaplan-Meier curves were compared using a log-rank test. Analysis of covariance was used to estimate the mean difference in the EQ-5D-5L visual analogue scale at 12 weeks, adjusting for baseline values. The secondary outcomes were analyzed using linear or logistic regression models. The descriptive component of the EQ-5D-5L questionnaire was analyzed without conversion into utilities by summing the health states (1 to 5, lower is better) across 5 dimensions and estimating the baseline-adjusted difference in means of the treatment groups. We estimated the hazard ratios for individual components of major adverse cardiovascular events. We also examined the clinical outcomes and adherence to Yoga-CaRe intervention stratified by key subgroups of patients (age, sex, and with comorbidities). The changes in EQ-5D-5L individual dimensions at 3 months were analyzed using 2 approaches. First, following a simpler methodology, the proportion of patients with some problems and the changes at 3 months were compared. Second, we categorized the changes in the individual dimensions as no change, improved, or worsened and carried out multinomial logistic regression model to estimate the treatment difference.

To evaluate the clinical implications of the magnitude of the change in self-rated health, we categorized EQ-5D-5L visual analogue scale at 12 weeks following a previously reported model (≤60 as poor self-rated health and >60 as good self-rated health) and commonly accepted model for minimum clinically important difference (≤10-point change as no change, more than 10-point increase at 12 weeks as improved, and decrease of more than 10 points as worsened) (22,23). In the first model, the treatment difference was estimated using logistic regression adjusting for baseline values, and in the second model, a multiple logistic regression model was used.

Similarly, we categorized return to pre-infarct activities following a previously reported model after normalizing the scores to 100 (100 as complete reintegration, 60 to 99 as mild to moderate issues, and <60 as poor reintegration) and the treatment difference was estimated using multiple logistic regression (24).

We examined clinical outcomes and adherence to Yoga-CaRe intervention stratified by key subgroups of patients (e.g., age, sex, physical activity, and comorbidities). Also, we examined effect modification by study center. We explored the effects of adherence to intervention by comparing hazards of incidence major adverse cardiovascular events for those who were above or below the median for attendance at direct contact sessions or self-practice at home (using the same statistical methods as primary outcome). We confirmed these results by splitting the follow-up time into weekly and 3-monthly intervals, and treating attendance at direct contact sessions or regular practice at home as time-varying exposures, respectively.

RESULTS

PATIENTS. Of the 6,737 patients screened for eligibility between August 2014 and March 2018, 3,959 were eligible and randomly assigned to receive Yoga-CaRe (n = 1,970) or enhanced standard care (n = 1,989) (see Supplemental Figure 1 for CONSORT diagram). The mean age of randomized patients was 53.4 ± 10.9 years, of which 14% were women. At the time of admission, 22% of the patients had a prior history of coronary heart disease. Angiography was performed in 80% of the patients and 61% underwent a revascularization procedure during the index admission. More than 90% of patients were receiving ≤2 standard cardiovascular medications at hospital discharge. The baseline characteristics of the 2 treatment groups are shown in **Table 1**.

CLINICAL OUTCOMES. After excluding 38 patients (17 in Yoga-CaRe group and 21 in enhanced standard care group) who could not be contacted at all after randomization, data on 3,921 (99%) patients were available for analyses. Those who were lost to follow-up subsequently (n = 48) or withdrew consent for further participation (n = 24) were included in the intent-to-treat analyses until the last follow-up. During a median follow-up of 21.6 months, the first occurrence of a major adverse cardiovascular event (composite of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, or emergency cardiovascular hospitalization) was recorded for 131 patients in the Yoga-CaRe group and 146 patients in the enhanced standard care group (6.7% vs. 7.4%; hazard ratio with Yoga-CaRe: 0.90; 95% confidence interval [CI]: 0.71 to 1.15; p = 0.41) (**Table 2, Figure 1,**

Central Illustration). The self-rated health (visual analogue scale of EQ-5D-5L) at 12 weeks was 77 points in the Yoga-CaRe group and 75.7 points in the enhanced standard care group (baseline-adjusted difference in mean in favor of Yoga-CaRe: 1.50; 95% CI: 0.53 to 2.48; p = 0.002) (**Table 2, Central Illustration**).

The return to pre-infarct activities score (Reintegration to Normal Living Index) at 12 weeks was 88.3 in the Yoga-CaRe group and 87.0 in the enhanced standard care group (difference in mean in favor of Yoga-CaRe group: 1.30; 95% CI: 0.06 to 2.54; p = 0.039). There was no difference in tobacco cessation or medication adherence at 12 weeks between the treatment groups (**Table 2**). There was no difference in serious adverse events between the treatment groups and no adverse events were reported during the Yoga-CaRe sessions (**Table 2**).

In nonprotocol defined analysis of EQ-5D-5L data, the Yoga-CaRe program reduced the odds of having poor self-rated health at 12 weeks more than the enhanced standard care (odds ratio: 0.73; p < 0.001). In the second model, improvements by 10 points in self-rated health was higher in the Yoga-CaRe group (relative risk ratio: 1.26; 95% CI: 1.10 to 1.46; p < 0.001). The Yoga-CaRe group had lower risk of poor reintegration at 12 weeks (relative risk ratio: 0.72; 95% CI: 0.56 to 0.92; p = 0.001).

There was no treatment difference in the incidence of individual components of major adverse cardiovascular events, although the Yoga-CaRe group had fewer cardiovascular hospitalizations. In exploratory subgroup analyses, greater reductions in hazards of major adverse cardiovascular events were noted in patients with pre-existing coronary heart disease and those without diabetes (**Figure 2**). We found no evidence of interaction by study center (p = 0.25). Of a total of 13 direct contact sessions, patients in the Yoga-CaRe group attended a median of 10 (interquartile range: 6 to 13) sessions; there was no difference in attendance at Yoga-CaRe sessions by sex or age of the participants.

The percentage of people reporting some problems in all the individual dimensions at 12 weeks decreased from baseline in both the groups with higher reductions in the Yoga-CaRe group. Also, the odds of worsening in the individual domains were lower in the Yoga-CaRe group. However, these differences did not reach statistical significance (Supplemental Tables 5 to 7).

EFFECT OF ADHERENCE TO INTERVENTION (NONPROTOCOL SPECIFIED EXPLORATORY ANALYSES). Those who were above the median for attendance at direct contact sessions (10 of 13) or self-practice at home (more than 30 min per day) had a lower incidence of major adverse cardiovascular events as compared with the enhanced standard care group (Supplemental Figures 2 and 3). In analyses treating attendance at direct contact sessions or self-practice at home as time-varying exposures, the hazard ratios for those achieving the median number of direct contact sessions or time practicing at home were 0.70 (95% CI: 0.53 to 0.93) and 0.64 (95% CI: 0.49 to 0.84), respectively.

TABLE 1 Baseline Characteristics of the Trial Participants

	Yoga-CaRe (n = 1,970)	Enhanced Standard Care (n = 1,989)
Age, yrs	53.4 ± 11.0	53.4 ± 10.8
Female	271 (13.8)	280 (14.1)
Formal education >10 yrs	1,154/1,966 (58.7)	1,213/1,986 (61.1)
Medical history at admission		
Coronary heart disease*	438/1,967 (22.3)	421/1,988 (21.2)
Diabetes mellitus	551/1,962 (28.1)	578/1,988 (29.1)
Hypertension	591/1,964 (30.1)	571/1,987 (28.7)
Congestive heart failure	3/1,969 (0.2)	4/1,988 (0.2)
Chronic kidney disease	7/1,960 (0.4)	6/1,880 (0.3)
Stroke	0/1,969 (0)	2/1,988 (0.1)
Current tobacco use	610/1,967 (31.0)	592/1,986 (29.8)
Current alcohol use	385/1,968 (19.6)	400/1,985 (20.2)
Physical inactivity	1,059/1,966 (53.9)	1078/1,984 (54.3)
Clinical presentation of myocardial infarction		
Multivessel disease on angiography	647/1,485 (43.6)	672/1,514 (44.4)
Anterior/anterolateral infarction	961/1,684 (57.1)	989/1,710 (57.8)
ST-segment elevation	1,478/1,970 (75.0)	1,511/1,988 (76.0)
Management at discharge		
Received percutaneous coronary intervention	1,128/1,967 (57.4)	1,156/1,988 (58.2)
Use of antiplatelet agent	1,940/1,969 (98.5)	1,960/1,987 (98.6)
Use of statin	1,836/1,969 (93.3)	1,851/1,987 (93.2)
Use of beta-blocker	1,233/1,969 (62.6)	1,244/1,987 (62.6)
Use of ACE inhibitor or ARB	1,013/1,969 (51.4)	982/1,987 (49.4)
Self-rated health†	66.3 ± 17.3	66.7 ± 17.0

Values are mean ± SD, n (%), or n/N (%). *Diagnosis of angina or myocardial infarction or revascularization procedure. †Visual analogue scale of European Quality of Life (EQ-5D-5L) (18).

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; Yoga-CaRe = yoga-based cardiac rehabilitation.

DISCUSSION

In this randomized controlled trial conducted, a yoga-based cardiac rehabilitation program was found to be safe and effective in improving quality of life and return to pre-infarct activities after acute myocardial infarction. Incidence of major adverse cardiovascular events was lower in patients enrolled in the Yoga-CaRe program, but the study lacked statistical power to show a difference in major adverse cardiovascular events.

TABLE 2 Study Outcomes

	Yoga-CaRe (n = 1,953)	Enhanced Standard Care (n = 1,968)	Effect Variable	Unadjusted Effect (95% CI)	p Value
Primary outcomes					
MACE (composite of death, nonfatal myocardial infarction, nonfatal stroke, or emergency cardiovascular hospitalization)*	131 (6.7)	146 (7.4)	Hazard ratio	0.90 (0.71 to 1.15)	0.41
Self-rated health at 12 weeks†	77.0 ± 16.8	75.7 ± 17.8	Difference in means	1.50 (0.53 to 2.48)	0.002
Secondary outcomes					
Return to pre-infarct activities at 12 weeks‡	88.3 ± 18.9	87.0 ± 20.1	Difference in means	1.30 (0.06 to 2.54)	0.039
High medication adherence at 12 weeks§	1,199 (64.6)	1,210 (64.3)	Odds ratio	1.01 (0.88 to 1.16)	0.88
Tobacco cessation at 12 weeks‖	449 (76.2)	445 (77.5)	Odds ratio	0.93 (0.71 to 1.22)	0.60
Other outcomes					
Death from any cause*	77 (3.9)	77 (3.9)	Hazard ratio	1.01 (0.74 to 1.39)	0.95
Nonfatal myocardial infarction*	13 (0.7)	15 (0.8)	Hazard ratio	0.88 (0.42 to 1.84)	0.73
Nonfatal stroke*	4 (0.2)	3 (0.2)	Hazard ratio	1.34 (0.30 to 6.00)	0.70
Emergency cardiovascular hospitalization*	48 (2.5)	59 (3.0)	Hazard ratio	0.82 (0.56 to 1.20)	0.31
Health state at 12 weeks¶	6.3 ± 2.9	6.5 ± 3.1	Difference in means	0.10 (−0.10 to 0.07)	0.23
Safety data					
Serious adverse events (noncardiac hospitalizations)	24 (1.2)	26 (1.3)	Odds ratio	0.93 (0.53 to 1.63)	0.80

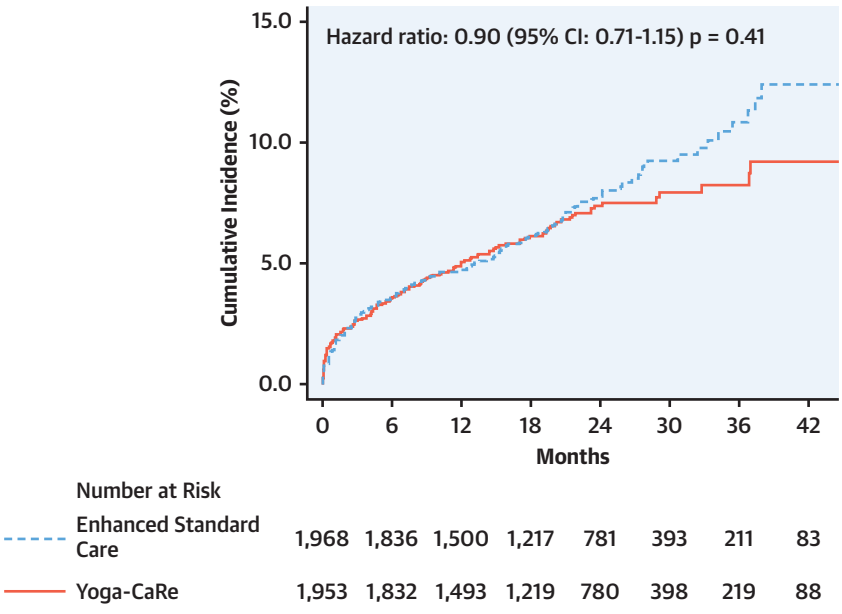
Values are n (%) or mean ± SD. *Event rates were based on Kaplan-Meier estimates in time-to-event analysis over the study follow-up period (median 21.6 months). Hazard ratio for first major adverse cardiovascular event was determined using a Cox proportional hazards model and the p values were calculated by using a log-rank test. †Self-rated health measured by visual analogue scale of the European Quality of Life questionnaire (EQ-5D-5L) (values from 0–100, higher is better) (18). Analysis of covariance was used to estimate the difference in mean quality of life of treatment groups at 12 weeks, adjusting for baseline values (n = 1,770 for Yoga-CaRe group, n = 1,786 for enhanced standard care group). ‡Return to pre-infarct activities was measured by Reintegration to Normal Life Index questionnaire (values from 0–110, higher is better) (19). Difference in means was estimated using linear regression (n = 1,886 for Yoga-CaRe, n = 1,923 for enhanced standard care group). §Medication adherence was derived by summing the individual items from 8-item questionnaire (values from 0 to 8) and categorized into 2 groups: high adherence (score = 0) and low adherence (score ≥1) (20). Odds ratio was estimated using logistic regression (n = 1,857 for Yoga-CaRe, n = 1,881 for enhanced standard care group). ‖Tobacco cessation was defined as cessation of tobacco use (any form) at 12 weeks among those using tobacco at baseline (n = 589 for Yoga-CaRe, n = 574 for enhanced standard care group). Odds ratio was estimated using logistic regression. ¶Health state was derived by summing the individual health states from descriptive components (mobility, self-care, usual activities, pain, anxiety/depression) of the European Quality of Life (EQ-5D-5L) questionnaire (values from 5 to 25). Analysis of covariance was used to estimate the difference in mean health state of treatment groups at 12 weeks, adjusting for baseline values (n = 1,769 for Yoga-CaRe, n = 1,791 for enhanced standard care group).

CI = confidence interval; MACE = major adverse cardiovascular event; Yoga-CaRe = yoga-based cardiac rehabilitation.

COMPARISON WITH PREVIOUS RESEARCH. There have been few small-scale trials of yoga-based cardiac rehabilitation and these have also reported improvements in functioning, quality of life, and recurrent cardiac events. The Lifestyle Heart Trial (n = 48), conducted in the late 1980s, reported improvements in cardiovascular risk factors and reduction in total number of cardiovascular events and need for revascularization over a 5-year follow-up period after a lifestyle modification program that included yoga (12). The PrimeTime trial (n = 28) found improvements in psychosocial measures of self-efficacy, perceived social support, and ability to cope with stress following a lifestyle intervention including yoga (14). In another trial from India (n = 42), a cardiac rehabilitation program that included yoga was associated with greater reductions in cardiovascular risk factors, need for revascularization procedures and size of atherosclerotic lesions on coronary angiography at 1 year, when compared with controls (13).

Our findings are also broadly consistent with trials of conventional exercise-based cardiac rehabilitation programs (25,26). The most recent systematic review of exercise-based cardiac rehabilitation identified 63 trials (n = 14,486) (3). In trials with medium-term follow-up, exercise-based cardiac rehabilitation reduced cardiovascular mortality (risk ratio: 0.74; 95% CI: 0.64 to 0.86) and hospital admissions (risk ratio: 0.82; 95% CI: 0.70 to 0.96), but not total mortality or myocardial infarction, when compared with no-exercise controls. Improvements in self-rated health were also found in most trials that collected these data (total 20 trials, combined n = 5,060), although a wide range of measures were used and the 2 that used the European Quality of Life did not show a difference. Individual trials, including the 2 largest trials that together contributed 30% of the data to the systematic review, also could not find conclusive evidence of benefit. The World Health Organization study (N = 3,184 from Europe) reported risk ratios of 0.91 (95% CI: 0.75 to 1.10) for total mortality and 1.10 (95% CI: 0.85 to 1.41) for myocardial infarction (27), whereas RAMIT (Rehabilitation after myocardial infarction trial) (N = 1,813 from the United Kingdom) reported risk ratios of 1.02 (95% CI: 0.87 to 1.18) for total mortality and 0.94 (95% CI: 0.63 to 1.39) for

FIGURE 1 Yoga-CaRe Versus Enhanced Standard Care on Major Cardiovascular Events



Cumulative incidence of major adverse cardiovascular events (composite of death, nonfatal myocardial infarction, nonfatal stroke, or emergency cardiovascular hospitalization) in the study groups. Hazard ratio for first major adverse cardiovascular event was determined using a Cox proportional hazards model and the p value used a log-rank test. Yoga-CaRe = yoga-based cardiac rehabilitation.

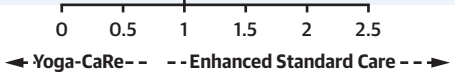
myocardial infarction, and no difference in self-rated health measured by the Short Form 36 (25). Reviews of observational (service use) data from the United States confirm the findings from the trial data, with continued benefits of cardiac rehabilitation despite improvements in cardiac care (5,28).

POTENTIAL MECHANISMS. The potential benefits of the Yoga-CaRe program could largely be attributed to meeting the core objectives of conventional cardiac rehabilitation programs: providing a structured program of exercise and support to optimize physical and psychosocial functioning, and improve health behaviors to slow disease progression. Given the low intensity of exercise in Yoga-CaRe, improvements in cardiac capacity and endorphin-mediated improvements in mood are expected to be lower than aerobic exercise. On the other hand, increasing evidence suggests that breathing movements, meditation, and stimulation of proprioceptors with stretching movements of yoga may be associated with vascular and mental health benefits through other pathways, such as the stimulation of parasympathetic nervous system (e.g., leading to improvements in heart rate variability and vascular tone through greater baroreceptor sensitivity), reduction in stress and its downstream vascular and endocrine effects (mediated by hypothalamic-pituitary axis; e.g., lower cortisol and reduced renin activity), and changes in neurotransmitters (e.g., increase in serotonin and decrease in dopamine) affecting mood and self-efficacy (29–33). The Yoga-CaRe group showed a greater improvement in self-rated health and reintegration to normal life, suggesting that it may operate, at least in part, through psychosocial pathways, although a bidirectional relationship between psychosocial and physical functioning in cardiac rehabilitation is previously reported (34). We did not find a difference in medication adherence or tobacco cessation between the treatment groups. Medication adherence and tobacco cessation were relatively high in both treatment groups, suggesting that lifestyle advice provided to the control arm during educational sessions may have attenuated the observed effects of the intervention.

STUDY LIMITATIONS. First, in common with previous trials of cardiac rehabilitation, our study was underpowered (43% study power based on original assumptions) for the composite outcome because of a

FIGURE 2 Hazard Ratios of Major Adverse Cardiovascular Event (Composite of Death, Nonfatal Myocardial Infarction, Nonfatal Stroke or Emergency Cardiovascular Hospitalization) for Key Subgroups of Patients

Subgroup	Yoga-CaRe	Enhanced Standard care	Hazard Ratio [95% CI]	p Value for Interaction
Age				
<65 Years	74/1,598 (4.6)	97/1,627 (6.0)	0.77 (0.57-1.05)	0.63
≥65 Years	27/337 (8.0)	29/339 (8.6)	0.9 (0.53-1.52)	
Sex				
Male	85/1,673 (5.1)	102/1,692 (6.0)	0.84 (0.63-1.12)	0.53
Female	16/262 (6.1)	24/274 (8.8)	0.67 (0.35-1.26)	
ST-segment elevation				
No	32/484 (6.6)	38/474 (8.0)	0.77 (0.48-1.23)	0.83
Yes	69/1,451 (4.8)	88/1,492 (5.9)	0.82 (0.6-1.12)	
Morphology				
Single Vessel Disease	34/829 (4.1)	51/839 (6.1)	0.66 (0.43-1.02)	
Double Vessel Disease	27/391 (6.9)	21/409 (5.1)	1.36 (0.77-2.4)	0.05
Triple Vessel Disease	11/243 (4.5)	25/253 (9.9)	0.44 (0.21-0.89)	0.3
Coronary Artery Disease				
No	79/1,499 (5.3)	84/1,549 (5.4)	0.98 (0.72-1.33)	0.02
Yes	22/431 (5.1)	42/415 (10.1)	0.49 (0.29-0.81)	
Diabetes				
No	58/1,394 (4.2)	88/1,396 (6.3)	0.65 (0.47-0.91)	0.03
Yes	43/534 (8.1)	38/569 (6.7)	1.2 (0.78-1.86)	
Hypertension				
No	63/1,354 (4.7)	85/1,402 (6.1)	0.76 (0.55-1.05)	0.54
Yes	38/575 (6.6)	41/562 (7.3)	0.9 (0.58-1.4)	
Revascularization				
No	45/760 (5.9)	59/740 (8.0)	0.75 (0.51-1.11)	0.65
Yes	56/1,075 (4.8)	67/1,226 (5.5)	0.85 (0.6-1.21)	
Physical Activity				
Physically Inactive	74/1,048 (7.1)	75/1,064 (7.1)	1.03 (0.74-1.43)	0.32
Moderate to high active	57/903 (6.3)	69/900 (7.7)	0.84 (0.6-1.19)	

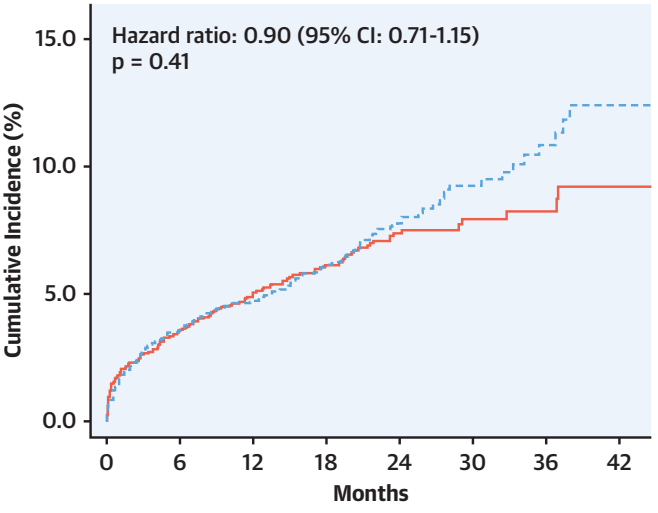


Event rates were based on Kaplan-Meier estimates in time-to-event analysis over the study follow-up period (median 21.6 months). Hazard ratio for first major adverse cardiovascular event was determined using a Cox proportional hazards model and the p values were calculated by using a log-rank test. CI = confidence interval; Yoga-CaRe = yoga-based cardiac rehabilitation.

lower than anticipated event rate (3). This may have been because of improvements in cardiac care in India over the past decades. More than 90% of patients were receiving ≤2 standard cardiovascular medications at hospital discharge in our trial. Our planned follow-up of the trial participants for 2 more years may provide evidence that is more conclusive. Second, the trial population was relatively young and predominantly male. This may reflect a combination of local epidemiology (the average age of myocardial infarction patients is ~10 years younger in India) (35), and the reluctance of recruiting clinicians and patients and their family members to enroll the elderly and women in trials (3). Although this is unlikely to affect the internal validity of the trial results, caution should be exercised when generalizing the findings to

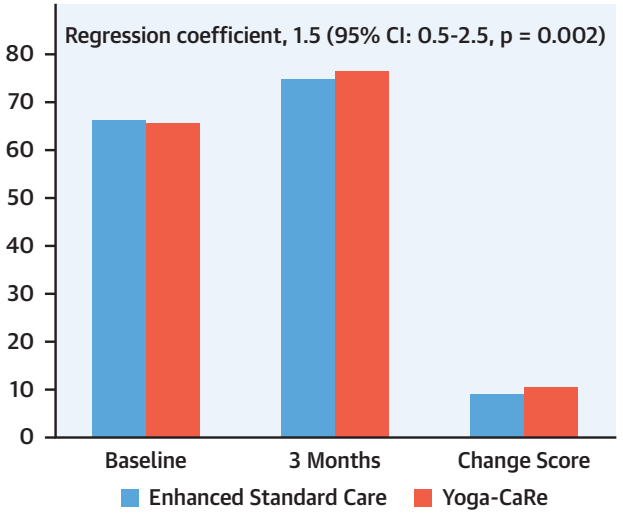
CENTRAL ILLUSTRATION **Yoga-Based Cardiac Rehabilitation Versus Enhanced Standard Care in Acute Myocardial Infarction**

Co-Primary Outcome 1: Major Adverse Cardiovascular Events



Number at Risk								
Enhanced Standard Care	1,968	1,836	1,500	1,217	781	393	211	83
Yoga-CaRe	1,953	1,832	1,493	1,219	780	398	219	88

Co-Primary Outcome 2: Self-Rated Health (EQ-VAS Score)



Major adverse cardiovascular events (composite of all-cause mortality, myocardial infarction, stroke or emergency cardiac hospitalization) over a median follow-up of 22 months: Enhanced standard care - 7.1% vs. Yoga-CaRe - 6.5%

Self-rated health at 12 weeks: Enhanced standard care - 75.7 vs. Yoga-CaRe - 77

Prabhakaran, D. et al. J Am Coll Cardiol. 2020;75(13):1551-61.

Cumulative incidence of major adverse cardiovascular event (composite of death, nonfatal myocardial infarction, nonfatal stroke, or emergency cardiovascular hospitalization) in the study groups. Event rates were based on Kaplan-Meier estimates in time-to-event analysis over the study follow-up period (median 21.6 months). Hazard ratio for first major adverse cardiovascular event was determined using a Cox proportional hazards model and the p value used a log-rank test. Self-rated health was assessed by the visual analogue scale of the European Quality of Life (EQ-5D-5L) questionnaire at baseline and at 12 weeks. Change score = 12 weeks minus baseline. CI = confidence interval; EQ-VAS = European Quality of Life visual analogue scale; Yoga-CaRe = yoga-based cardiac rehabilitation.

older and female patients, as well as patients from other countries in which yoga may be less acceptable to patients. Once enrolled, we noted no difference in adherence or clinical outcomes by age group and sex, confirming our hypothesis that yoga-based cardiac rehabilitation programs could contribute to improved adherence among women and the elderly. Third, conventional exercise-based cardiac rehabilitation programs were lacking in most centers and it was not feasible for us to introduce them as part of the trial precluding advice on their relative benefits. Fourth, in keeping with our scalability objectives, we evaluated a low-intensity intervention (13 direct contact sessions as opposed to 36 sessions in many U.S. programs) and made no effort to improve adherence to the intervention, which may have underestimated the potential benefits of Yoga-CaRe (as suggested by the results of exploratory analyses). However, the results of exploratory analysis should be interpreted with caution, as it breaks the randomized group and may be prone to selection bias. Finally, the inherent limitation of the tools used for assessing quality of life and return to pre-infarct activities, such as ceiling effect and moderate responsiveness, in the short term might have underestimated the effect of the Yoga-CaRe program. However, the nonprotocol-defined analyses of self-rated health involving categorical approaches following previously reported methods provide a hypothetical framework for the beneficial effects of Yoga-CaRe and support the clinical and public health importance of our findings.

CLINICAL PRACTICE AND POLICY IMPLICATIONS. Yoga-CaRe has the potential to address the unmet need of disadvantaged groups worldwide. In low- and middle-income countries, such as India, conventional exercise-based cardiac rehabilitation programs are lacking, as most hospitals cannot afford the infrastructure and recruiting large multidisciplinary teams is challenging (6,7). Hiring a single yoga teacher at the cost of approximately USD $250 per month (2018 prices), which is within the reach of most medium-sized hospitals in India, could meet their entire rehabilitation needs. It has been estimated that approximately 1.5 million patients experience myocardial infarction each year in India, which highlights the considerable potential for saving lives and reducing economic burden. In high-income countries, such as the United States and United Kingdom, the primary challenge is low enrollment and adherence among certain subgroups (e.g., elderly, women, low-income). Distance to a rehabilitation facility also can be a barrier to attendance in many settings. Given the lack of direct comparison with yoga-based cardiac rehabilitation and a large body of existing evidence underpinning its use, we recommend that, wherever available, conventional exercise-based cardiac rehabilitation should remain the treatment of choice, and Yoga-CaRe should be reserved as a treatment option for individual patients who choose not to enroll or adhere to conventional cardiac rehabilitation programs (4,5). A randomized trial comparing conventional and yoga-based cardiac rehabilitation may help to inform practice in this regard.

CONCLUSIONS

The results of this trial show that a yoga-based cardiac rehabilitation program can safely improve self-rated health and return to pre-infarct activities after acute myocardial infarction, although the trial lacked statistical power to provide evidence of difference in major adverse cardiovascular events.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Yoga-based cardiac rehabilitation is better than no rehabilitation after acute myocardial infarction, improving self-rated health and return to pre-infarct activities.

TRANSLATIONAL OUTLOOK: Longer-term comparative studies are needed to evaluate the utility of yoga-based cardiac rehabilitation in settings in which conventional exercise-based programs are not available or applicable.

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KEY WORDS acute myocardial infarction, cardiac rehabilitation, coronary artery disease, rehabilitation, secondary prevention, yoga

APPENDIX For a complete list of investigators and members of various committees, supplemental figures, and tables, please see the online version of this paper.