View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Repository@Nottingham

Effectiveness and cost-effectiveness of a Yoga-based Cardiac Rehabilitation (Yoga-CaRe) program following acute myocardial infarction:

Study rationale and design of a multi-centre randomized controlled trial

Background

Coronary artery disease (CAD) is the leading cause of death and disability in India. [1,2] The psychosocial and economic aspects of CAD are particularly important, as CAD typically manifests at younger ages (<55 years) in previously healthy adults. These adults experience considerable difficulty in accepting their illness, resulting in reduced enthusiasm to engage with the family and return to economically productive activity. [3] Hence, there is a compelling need for effective secondary prevention interventions, aimed at improving both the duration and the quality of life of those affected.

Cardiac rehabilitation (CR) is the process of restoring desirable levels of physical, social, and psychological functioning after the onset of CAD or after interventions for CAD. It is typically achieved through a program of exercise and information sessions. CR programs for patients with CAD have been shown to reduce mortality and hospital admissions, improve quality of life, and reduce the costs associated with care. [4–6] However, CR programs are unavailable to most patients in India) due to high costs and skills required for multidisciplinary CR teams. [7] The WHO Global action plan for the prevention of non-communicable diseases (NCDs) has advocated for harnessing the potential of traditional and complementary therapies because of their potentially lower costs and greater cultural acceptability. [8] Although alternate

models of CR based on complementary and alternative therapies have been proposed, their clinical effectiveness and safety is yet to be established. [9,10] Low-cost and sustainable CR programs based on local traditional practices could address the unmet need of CR globally.

Yoga is an ancient Indian system of mind-body discipline, encompassing an array of philosophical precepts, mental attitudes and physical practices. [11] Although it is practiced in many forms, the most common ones incorporate elements of physical poses, breathing practices and meditation, and moderation in lifestyle including diet, stress and sleep and abstinence from smoking and alcohol. As such, it covers the core elements of a CR program: improved physical conditioning, stress reduction and lifestyle moderation. The structure of a yoga training program is also similar to CR (a series of exercise-cum-education sessions, but requires considerably fewer resources (i.e. a basic instructor). Yoga, therefore, could provide a useful framework on which to develop an economical CR program for India.

Strong rationale exists for the use of yoga in the prevention of cardiovascular diseases. Studies suggest yoga down-regulates effects of stress (primarily on blood pressure) mediated by hypothalamic-pituitary-adrenal axis (e.g. cortisol), specifically the renin-angiotensin system, and the sympathetic nervous system (e.g. improvement in baroreceptor sensitivity). [12–14] Variable improvements in functional capacity (e.g. ventricular structure/function), inflammatory markers, carotid intima-media thickness and other conventional cardiovascular risk factors (e.g. insulin, lipids) are also reported. [15] Also, yoga has been shown to improve health related quality of life in chronic diseases. [16–19] However, these studies have been limited by small sample sizes, lack of control groups and unmasked assessment of

outcomes. [20–22]. We therefore hypothesized that yoga could be an useful cardiac rehabilitation tool. We propose to evaluate this through a randomized control trial.

Methodology

Study design and recruitment strategy

This is a multi-center, single-blind, two-arm parallel group, randomized controlled trial (RCT) conducted across 24 cardiac centers in India. The study sites include a mix of public funded, teaching hospitals and private hospitals to allow recruitment of patients from a wide range of socio-economic backgrounds. As is typical of India, most (19/22 clinical sites) did not have existing formal CR programs. Patients are assessed for eligibility after signing a written informed consent form.

Inclusion and exclusion criteria

Inclusion criteria Patients are considered to be eligible for the study if they meet the following criteria:

1. Aged 18-80 years
2. Experienced first or subsequent AMI and survived to hospital discharge within 14 days of AMI. AMI confirmed by the World Health Organization 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 presence of either symptoms of myocardial infarction or changes in electrocardiogram). [23,24]
3. Willing and able to attend the complete hospital-based CR program on their own

Exclusion criteria Patients are ineligible if they meet any of the following criteria at screening:

1. Site investigators consider that the patient will be unable to complete the study and/or attend for follow-up
2. Regularly practice yoga i.e., more than 3 hours a week
3. Currently participating in any other clinical trials
4. Have any other diseases which limit their life to less than a year (e.g. severe valvular disease, recurrent ventricular arrhythmias, NYHA Class 4 heart failure, severe aortic incompetence, severe atrial fibrillation, cancers, and end-stage renal or liver disease

Randomization

Eligible and consenting patients are randomized (block randomization, stratified by age-band (< or ≥ 60 years) and gender) in a 1:1 ratio by a computer program centrally (Research coordinating center (RCC), New Delhi) using an interactive web response system (IWRS) and after collecting key identifying data.

We chose individual randomization (within centers) over cluster randomization (with centers as clusters) because we considered potential bias from differences in clinical practice between centers to be a more serious threat to study validity than contamination, particularly because Yoga-CaRe as a CR program would not be available externally, even if yoga classes could be.

Interventions:

Yoga-CaRe program

The Yoga-CaRe program was developed using a structured process. This included a literature review and qualitative and quantitative interviews with yoga experts, CR experts and patients with myocardial infarction to systematically identify and shortlist

appropriate yoga exercises and postures, breathing exercises, meditation and relaxation practices, and lifestyle changes, which were incorporated into a conventional CR framework. . The details of the CR program are under review for publication elsewhere. Briefly, it involves 13 hospital-based sessions spread over 3 months (**Table 1**). Patients are also encouraged to practice daily at home following the instructions provided in a DVD and booklet. The first two sessions are delivered individually, with the remaining in groups. The exercise-cum-education sessions involve a combination of exercises related to general physical conditioning, stress and relaxation (health rejuvenating exercises- around 10 minutes, yoga poses- 25 minutes, breathing exercises-15 minutes, meditation and relaxation practices- 15 minutes; and moderated discussion- 10 minutes), and some exercises believed to be of particular cardio-protective benefit in yogic texts. The lifestyle and other educational components are informed by yogic ideas but moderated by established scientific evidence. Spouses or care-givers are also encouraged to attend the sessions where possible and assist the participant at home.

Table 1 Model of Yoga-CaRe in relation to the standard four-phase model of CR

Phase	Yoga-CaRe
1 Inpatient/outpatient care	Week 1-2: Education session (Session 1) (one hour)
2 Formal outpatient CR program I	Week 3: Exercise session (Session 2) (30 minutes)
3 Formal outpatient CR program II	Weeks 5-7: Exercise-education sessions, twice per week (Sessions 3-8)* Weeks 8-12: Exercise-education sessions, once per week (Sessions 9-13)*

	(Each Session - 75 minutes including moderated discussion)
4 Long-term maintenance of lifestyle changes & self-practice of yoga at home	Weeks 13+: Maintenance of lifestyle changes & self-practice of yoga at home using the booklet & DVD provided

* In addition to the outpatient training visits, self-supervised sessions (1 hour) with DVD and book at home, 5-7 times per week

The practices are delivered by a trained Yoga-CaRe instructor (one instructor at each of the clinical site) with prior experience of yoga (at least one year training). Yoga-CaRe instructors received training in the delivery of the Yoga-CaRe program by our team of cardiologists, cardiac rehabilitation experts and yoga experts during an initial induction program followed by refresher training programs every 12 months. This also includes didactic lectures on anatomy and physiology of the cardiovascular system, communicating with patients, barriers and facilitators to cardiac rehabilitation program and importantly identifying warning signs or distress symptoms. In addition, manual for instructors was provided to the instructors in their local language. We are video-recording of 10 sessions in each of the participating centers and around 80 sessions are video-recorded; these are supplemented by direct observations of the sessions by the study team. Data on adherence to home-practices are collected by questionnaires completed during each follow-up session.

Control:

Enhanced standard care

Patients in the control group receive enhanced standard care in the form of educational advice with a leaflet, once before discharge from the hospital and

subsequently at weeks 5 and 12 (sessions 2 and 3) along with standard medical care as elsewhere in India but does not include rehabilitation [25]. The sessions are delivered in groups or individually by a different member of the team (not yoga instructor) to avoid contamination.

Outcome measures and data collection

Primary outcomes

The co-primary outcomes are cardiac mortality and morbidity over the follow-up period, and quality of life at 12 weeks.

The cardiac mortality and morbidity outcome is the time to first cardiovascular event which is a composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke, hospitalizations for emergency revascularization, unstable angina and heart failure. The documents related to the events such as death certificates, admission and discharge summary etc are prospectively collected and the outcomes are adjudicated by an Endpoint Adjudication Committee blinded to treatment allocation (Supplementary file).

The quality of life is assessed using the European Quality of Life questionnaire (EuroQol EQ-5D-5L) at 12 weeks. EQ-5D was chosen because it has been validated against longer and disease specific questionnaires in acute coronary syndrome patients undergoing cardiac rehabilitation and found to be valid, reliable and responsive. [26] In addition, it is brief (important for telephonic completion) and local translation versions available in all major Indian languages. Those not appearing for the clinic visit have their assessment completed telephonically. The timing of this

assessment is chosen so as to capture both the speed and completeness of functional recovery.

Secondary outcomes

Data on any revascularization procedures [coronary artery bypass surgery (CABG) and percutaneous coronary interventions (PCI)] during the trial period are collected using the same process as the cardiovascular events.

Data on return to pre-infarct daily activities is assessed by Reintegration to Normal Living Index (RNLI). [27] The questionnaire contains 11 statements and the responses are evaluated in a visual analogue scale. Those not appearing for the clinic visit have their assessment completed telephonically.

Tobacco cessation is based on self-reports. In a random subset of about 5% of the trial population, salivary samples are collected to validate self-reports.

Adherence to prescribed medication is assessed by Morisky Medication Adherence Scale (MMAS). MMAS has a high sensitivity and has been used in Indian settings in the past.. [28]

Data on cognitive function is being collected using the Montreal Cognitive Assessment (MoCA), and anxiety and depression using Hospital Anxiety and Depression Scale (HADS), in a subset of participants (n=400). MoCA and HADS are validated and widely accepted tools for assessing cognitive assessment and anxiety respectively. [29,30]

Every participant will be followed for a minimum of six months till end of the trial. The end of study differs for each participant depending on the time they were enrolled into the study. The site coordinators upload the data collected from participants

through electronic case report forms to the central database located in the Research Coordinating Centre (RCC). The database has a limited access password protected system and constructed with built-in range checks to avoid errors in data. Also, the data are cross-checked against the source documents during regular on-site monitoring visits and regular central statistical monitoring to detect outliers and data discrepancies. At the clinical site, collected data is protected in fire-proof and locked safes. All the participant data will be de-identified in the final dataset and will be made available for bonafide researchers upon request to the investigators.

Table 2: Schema of data collection in Yoga-CaRe trial

Outcome measure	Time of data collection
Primary outcome measures 1. Cardiovascular events 2. Quality of life	 1. Every three months till the end of the study 2. Baseline, three months, nine months and end of study.
Secondary outcome measures 1. Need for revascularization procedures 2. Return to pre-infarct daily activities 3. Tobacco cessation	 1. Every three months till the end of the study 2. Baseline, three months, nine months and end of study. 3. Baseline, three months, nine months and end of study.

4. compliance to medications 5. Costs of care 6. Cognitive function, anxiety and depression	4. Baseline, three months, nine months and end of study. 5. Every three months till the end of the study 6. Baseline, three months, nine months and end of study

Sample size estimation

The required sample size was estimated using incidence data from a multinational registry that includes India (cumulative annual incidence rate of ~20-25% for a composite outcome of all-cause mortality, nonfatal MI and stroke, following AMI) [31] and effectiveness data from systematic reviews of CR trials (a 20-25% reduction in adverse vascular outcomes). The total sample required was initially estimated as 3,102, assuming 20% annual incidence in the control arm and a 20% effect size at a median follow-up of 12 months, a 10% loss to follow-up, at 80% power and 5% significance level. Estimation was based on time-to-first-event data (censoring the patient subsequently). Midway through the study, the sample size was re-estimated to account for a lower observed incidence of outcomes, which is consistent with a rapid improvement in cardiac care in India over the last decade. We therefore proposed to recruit 5000 patients; however, the Data Monitoring and Ethics committee recommended stopping recruitment at 4000 and extending the study follow-up after reporting the results until this point (including the minimum 6 months follow-up).

A considerably smaller sample is required to detect differences in quality of life; a total sample of 818 (409 in each group) would be adequate to detect a 5% difference in the mean EQ-5D scores, with 95% confidence.

Analysis of outcomes

The observed difference in the hazard of the first adverse vascular event (censoring subsequent events) between the treatment and the control arm will be assessed by fitting a Cox proportional hazards model. Cardiovascular events will be estimated by the Kaplan–Meier method and comparisons made by the Log rank test. The primary analysis for the quality of life will be assessed by estimating the difference between the treatment arms in the change score from baseline to 12 weeks in health thermometer by fitting conventional regression models. Also, EQ-5D-5L index as a whole and its five dimensions will be analyzed as scaled outcomes and differences between treatment arms will be examined by fitting regression models.

All primary analyses will be on an intention to treat principle and will be unadjusted, and subsequently adjusted for covariates with baseline imbalances including centre. We will also report the per-protocol or on treatment analyses. For missing data, sensitivity analyses will be conducted for primary end points, including a complete case analysis and multiple imputations to evaluate the potential effect of missingness.

Economic analyses

We will calculate health expenditures and within-trial cost-effectiveness of the intervention compared to enhanced standard care using a health care system and

patient perspective as our base-case analysis, and a societal perspective in sensitivity analyses.

Health expenditures will include direct medical costs and implementation/delivery costs of the intervention (i.e. costs attributable to research activities will be excluded) from our clinic and study expenditures. We will estimate the incremental costs of intervention (outpatient visits, medications, in-patient hospitalizations, and indirect medical costs) compared to enhanced standard care group. Given that public and private clinics are participating in our trial, we will also report expenditures for interventions relative to enhanced standard care by type of clinic and cumulatively.

The primary outcome for cost-effectiveness will be major adverse cardiovascular events (MACE) averted and quality adjusted life years (QALYs) gained. Both MACE and QALY data are being collected over the trial duration. QALYs can be compared across interventions and countries (using a ceiling ratio [set cost per QALY value as a reference point]). Uncertainty around incremental costs and incremental outcomes (MACE averted and QALYs gained) will be estimated using non-parametric bootstrap methods.

A probabilistic decision analytic health state-transition model (Markov model) will be constructed to extrapolate the trial effects over patients' lifetime horizon. A hypothetical cohort of acute myocardial infarction patients with a given set of characteristics (e.g. age, comorbidities) will be followed until death over successive time cycles of set length (1 year). Where available, appropriate prognostic models will be used to predict the time-dependent risk of major adverse cardiovascular events. The incurred costs and health outcomes over the model time horizon will be summed and averaged for intervention and enhanced standard care groups and the

long-term incremental cost-effectiveness of intervention will be calculated. An annual discount rate of 3% will be applied to both costs and outcomes, which will be varied in sensitivity analyses. A range of scenario analyses will be conducted to investigate the influence of alternative assumptions on the base case results.

Ethical considerations and risks

The Institutional ethics committee (IEC) of the Centre for Chronic Disease Control and London School of Hygiene and Tropical Medicine and the ethics committee of the individual participating/clinical sites approved the study protocol. Although this is a behavioral intervention and yoga is inherently safe, there is a small risk of adverse event from inappropriate practice or exertion, particularly among those in a poor health state after their AMI. Patients are carefully selected with the help of site investigators who are physicians and Yoga-CaRe instructors are trained to adapt the program to the ability of the patient and anticipate the symptoms of AMI. Yoga sessions are held in the hospital premises and clinical investigators made aware of them. Any serious adverse events at the sites are notified to respective ethics committees and periodically to the Data Monitoring and Ethics Committee (DMEC), the Trial Operations Committee and the Trial Steering Committee. All team members involved in the study including the Yoga–CaRe instructors are trained in Good Clinical Practice guidelines.

Discussion

CR programs are an integral part of cardiovascular management globally. [32,33] They effectively reduce mortality (up to half) and morbidity, improve quality of life,

lower medical and social costs, and increase economic productivity, comparing favorably to effective pharmacological treatments for secondary prevention of AMI (e.g. statins and beta blockers) with minimal side effects. Yet, their uptake remains low. In low and middle income countries (LMICs) such as India, the cost and skills required for large multidisciplinary teams used to deliver established CR programs is prohibitive, making them un-scalable. Even in HICs where CR programs are universally available, uptake is often low, particularly among disadvantaged groups such as women, the elderly and minority ethnic groups, who find the gymnasium style exercise programs unappealing due to unfamiliarity and cultural and attitudinal reasons. Hence there is an urgent need to develop other forms of CR programs which are affordable and culturally acceptable (in LMICs) and offer a choice (in HICs). [7,34] Yoga-CaRe will address this unmet need if it is found to improve outcomes and is cost-effective, and may also instigate development of CR programs based on other cultural practices, such as the Chinese Tai Chi.

Strengths and limitations

Previous trials of CR in post MI patients have been relatively small randomizing up to a few hundred participants with exception of the WHO (1983) and West (2012) that randomized 3184 participants and 1813 participants respectively.[6] Also, most data are from the developed countries. Our trial will be considerably larger and will contribute to more than 20% of participants in meta-analyses of randomized trials of CR. Also, it is independently powered for policy relevant outcomes of clinical effectiveness. It is embedded within the typical healthcare system (mix of public and private) making findings generalizable, and has inbuilt economic data collection to undertake robust economic analyses to guide actions by policy makers and private healthcare providers. The intervention was designed to be extremely low cost and

scalable, ensuring immediate impact on policy and clinical practice. Conversely, the pragmatic design of the intervention (only a few supervised sessions) also precludes estimation of true efficacy of yoga for CR, increasing the likelihood of a false negative result. We lacked the resources to explore the role of specific mechanistic pathways that have been proposed for cardiovascular health effects of yoga. However, we have recently completed a separate parallel study on that question in the UK, which will be reporting its results soon.

Trial status

The trial commenced in August 2014 and will be completed by September 2018. A total of 4016 AMI patients have been recruited from 22 centers across India. The study results will be promulgated to the participating patients, physicians, yoga-instructors, policy makers and general population through policy briefs and research papers after March 2019.

Funding

The study is funded through a collaborative research grant from the Indian Council for Medical Research and Medical Research Council, UK. (ICMR -58/1/9/MRC-ICMR/2009/NCD-II and MRC- MR/J000175/1). The sponsors have no role in study design, data collection, management, analysis and interpretation of the data and dissemination of the results.

References

[1] GBD 2016 DALYs and HALE Collaborators, Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016., Lancet (London, England). 390 (2017) 1260–1344. doi:10.1016/S0140-6736(17)32130-X.

[2] India State-Level Disease Burden Initiative Collaborators, Nations within a nation: variations in epidemiological transition across the states of India, 1990-2016 in the Global Burden of Disease Study., Lancet (London, England). 390 (2017) 2437–2460. doi:10.1016/S0140-6736(17)32804-0.

[3] V.S. Ajay, D. Prabhakaran, Coronary heart disease in Indians: implications of the INTERHEART study., Indian J. Med. Res. 132 (2010) 561–6. http://www.ncbi.nlm.nih.gov/pubmed/21150008 (accessed January 4, 2018).

[4] R.S. Taylor, A. Brown, S. Ebrahim, J. Jolliffe, H. Noorani, K. Rees, B. Skidmore, J.A. Stone, D.R. Thompson, N. Oldridge, Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials., Am. J. Med. 116 (2004) 682–92. doi:10.1016/j.amjmed.2004.01.009.

[5] P.R. Lawler, K.B. Filion, M.J. Eisenberg, Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: A systematic review and meta-analysis of randomized controlled trials, Am. Heart J. 162 (2011). doi:10.1016/j.ahj.2011.07.017.

[6] L. Anderson, D.R. Thompson, N. Oldridge, A.-D. Zwisler, K. Rees, N. Martin, R.S. Taylor, Exercise-based cardiac rehabilitation for coronary heart disease, Cochrane Database Syst. Rev. (2016). doi:10.1002/14651858.CD001800.pub3.

[7] K. Madan, A.S. Babu, A. Contractor, J.P.S. Sawhney, D. Prabhakaran, R. Gupta, Cardiac Rehabilitation in India, Prog. Cardiovasc. Dis. 56 (2014) 543–550. doi:10.1016/j.pcad.2013.11.001.

[8] WHO, Global action plan for the prevention and control of noncommunicable diseases 2013-2020., World Heal. Organ. (2013) 102. doi:978 92 4 1506236.

[9] H.M. Arthur, C. Patterson, J.A. Stone, The role of complementary and alternative therapies in cardiac rehabilitation: a systematic evaluation, Eur.J Cardiovasc Prev.Rehabil. 13 (2006) 3–9. doi:10.1097/01.hjr.0000198917.67987.f8.

[10] S.L. Grace, K.I. Turk-Adawi, A. Contractor, A. Atrey, N. Campbell, W. Derman, G.L. Melo Ghisi, N. Oldridge, B.K. Sarkar, T.J. Yeo, F. Lopez-Jimenez, S. Mendis, P. Oh, D. Hu, N. Sarrafzadegan, Cardiac rehabilitation delivery model for low-resource settings., Heart. 102 (2016) 1449–55. doi:10.1136/heartjnl-2015-309209.

[11] G. Feuerstein, The deeper dimension of Yoga : theory and practice, Shambhala, 2003. https://www.shambhala.com/the-deeper-dimension-of-yoga-473.html (accessed January 4, 2018).

[12] A. Ross, S. Thomas, The health benefits of yoga and exercise: a review of comparison studies., J. Altern. Complement. Med. 16 (2010) 3–12.

doi:10.1089/acm.2009.0044.

[13] L. Nivethitha, A. Mooventhan, N. Manjunath, Effects of various Prāṇāyāma on cardiovascular and autonomic variables, Anc. Sci. Life. 36 (2016) 72. doi:10.4103/asl.ASL_178_16.

[14] A. Tyagi, M. Cohen, Yoga and heart rate variability: A comprehensive review of the literature., Int. J. Yoga. 9 (2016) 97–113. doi:10.4103/0973-6131.183712.

[15] M.C. Pascoe, I.E. Bauer, A systematic review of randomised control trials on the effects of yoga on stress measures and mood., J. Psychiatr. Res. 68 (2015) 270–82. doi:10.1016/j.jpsychires.2015.07.013.

[16] B. Hari Krishna, P. Pal, G.K. Pal, J. Balachander, E. Jayasettiaseelon, Y. Sreekanth, M.G. Sridhar, G.S. Gaur, Yoga improves quality of life and functional capacity in heart failure patients, Biomed. Res. 25 (2014) 178–182. http://biomedres.info/yahoo_site_admin/assets/docs/178-182-Bandi_Hari_Krishna.70223308.pdf.

[17] A.S. Levine, J.L. Balk, Yoga and quality-of-life improvement in patients with breast cancer: a literature review., Int. J. Yoga Therap. (2012) 95–9. http://www.ncbi.nlm.nih.gov/pubmed/23070679.

[18] B.S. Oken, D. Zajdel, S. Kishiyama, K. Flegal, C. Dehen, M. Haas, D.F. Kraemer, J. Lawrence, J. Leyva, Randomized, controlled, six-month trial of yoga in healthy seniors: effects on cognition and quality of life., Altern. Ther. Health Med. 12 (2006) 40–7. http://www.ncbi.nlm.nih.gov/pubmed/16454146.

[19] a Ziv, O. Vogel, D. Keret, S. Pintov, E. Bodenstein, K. Wolkomir, K. Doenyas,

Y. Mirovski, S. Efrati, Comprehensive Approach to Lower Blood Pressure (CALM-BP): a randomized controlled trial of a multifactorial lifestyle intervention., J. Hum. Hypertens. 27 (2013) 594–600. doi:10.1038/jhh.2013.29.

[20] S.C. Manchanda, R. Narang, K.S. Reddy, U. Sachdeva, D. Prabhakaran, S. Dharmanand, M. Rajani, R. Bijlani, Retardation of coronary atherosclerosis with yoga lifestyle intervention, J. Assoc. Physicians India. 48 (2000) 687–694. http://www.ncbi.nlm.nih.gov/pubmed/11273502.

[21] N. Raghuram, V.R. Parachuri, M. V Swarnagowri, S. Babu, R. Chaku, R. Kulkarni, B. Bhuyan, H. Bhargav, H.R. Nagendra, Yoga based cardiac rehabilitation after coronary artery bypass surgery: one-year results on LVEF, lipid profile and psychological states--a randomized controlled study., Indian Heart J. 66 (2014) 490–502. doi:10.1016/j.ihj.2014.08.007.

[22] R.H. Schneider, C.E. Grim, M. V Rainforth, T. Kotchen, S.I. Nidich, C. Gaylord-King, J.W. Salerno, J.M. Kotchen, C.N. Alexander, Stress reduction in the secondary prevention of cardiovascular disease: randomized, controlled trial of transcendental meditation and health education in Blacks., Circ. Cardiovasc. Qual. Outcomes. 5 (2012) 750–8. doi:10.1161/CIRCOUTCOMES.112.967406.

[23] S. Mendis, K. Thygesen, K. Kuulasmaa, S. Giampaoli, M. Mähönen, K. Ngu Blackett, L. Lisheng, Writing group on behalf of the participating experts of the WHO consultation for revision of WHO definition of myocardial infarction, World Health Organization definition of myocardial infarction: 2008-09 revision., Int. J. Epidemiol. 40 (2011) 139–46. doi:10.1093/ije/dyq165.

[24] K. Thygesen, J.S. Alpert, A.S. Jaffe, M.L. Simoons, B.R. Chaitman, H.D.

White, Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, H.A. Katus, B. Lindahl, D.A. Morrow, P.M. Clemmensen, P. Johanson, H. Hod, R. Underwood, J.J. Bax, R.O. Bonow, F. Pinto, R.J. Gibbons, K.A. Fox, D. Atar, L.K. Newby, M. Galvani, C.W. Hamm, B.F. Uretsky, P.G. Steg, W. Wijns, J.-P. Bassand, P. Menasché, J. Ravkilde, E.M. Ohman, E.M. Antman, L.C. Wallentin, P.W. Armstrong, M.L. Simoons, J.L. Januzzi, M.S. Nieminen, M. Gheorghiade, G. Filippatos, R. V. Luepker, S.P. Fortmann, W.D. Rosamond, D. Levy, D. Wood, S.C. Smith, D. Hu, J.-L. Lopez-Sendon, R.M. Robertson, D. Weaver, M. Tendera, A.A. Bove, A.N. Parkhomenko, E.J. Vasilieva, S. Mendis, Third universal definition of myocardial infarction., Circulation. 126 (2012) 2020–35. doi:10.1161/CIR.0b013e31826e1058.

[25] M.D. Huffman, P.P. Mohanan, R. Devarajan, A.S. Baldridge, D. Kondal, L. Zhao, M. Ali, M.N. Krishnan, S. Natesan, R. Gopinath, S. Viswanathan, J. Stigi, J. Joseph, S. Chozhakkat, D.M. Lloyd-Jones, D. Prabhakaran, Acute Coronary Syndrome Quality Improvement in Kerala (ACS QUIK) Investigators, Effect of a Quality Improvement Intervention on Clinical Outcomes in Patients in India With Acute Myocardial Infarction, JAMA. 319 (2018) 567. doi:10.1001/jama.2017.21906.

[26] B. Schweikert, H. Hahmann, R. Leidl, Validation of the EuroQol questionnaire in cardiac rehabilitation., Heart. 92 (2006) 62–7. doi:10.1136/hrt.2004.052787.

[27] S. Wood-Dauphinee, M.A. Opzoomer, J.I. Williams, B. Marchand, W.O. Spitzer, Assessment of global function: The Reintegration to Normal Living Index, Arch. Phys. Med. Rehabil. 69 (1988) 583–590.

http://www.ncbi.nlm.nih.gov/pubmed/3408328 (accessed January 11, 2018).

[28] S.J. Moon, W.-Y. Lee, J.S. Hwang, Y.P. Hong, D.E. Morisky, Accuracy of a screening tool for medication adherence: A systematic review and meta-analysis of the Morisky Medication Adherence Scale-8., PLoS One. 12 (2017) e0187139. doi:10.1371/journal.pone.0187139.

[29] C. Herrmann, International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results., J. Psychosom. Res. 42 (1997) 17–41. doi:10.1016/S0022-3999(96)00216-4.

[30] Z. Ismail, T.K. Rajji, K.I. Shulman, Brief cognitive screening instruments: an update., Int. J. Geriatr. Psychiatry. 25 (2010) 111–20. doi:10.1002/gps.2306.

[31] D. Prabhakaran, S. Yusuf, S. Mehta, J. Pogue, A. Avezum, A. Budaj, L. Cerumzynski, M. Flather, K. Fox, D. Hunt, L. Lisheng, M. Keltai, A. Parkhomenko, P. Pais, S. Reddy, M. Ruda, T. Hiquing, Z. Jun, Two-year outcomes in patients admitted with non-ST elevation acute coronary syndrome: results of the OASIS registry 1 and 2., Indian Heart J. 57 217–25. http://www.ncbi.nlm.nih.gov/pubmed/16196178 (accessed November 30, 2014).

[32] P.T. O'Gara, F.G. Kushner, D.D. Ascheim, D.E. Casey, M.K. Chung, J.A. de Lemos, S.M. Ettinger, J.C. Fang, F.M. Fesmire, B.A. Franklin, C.B. Granger, H.M. Krumholz, J.A. Linderbaum, D.A. Morrow, L.K. Newby, J.P. Ornato, N. Ou, M.J. Radford, J.E. Tamis-Holland, C.L. Tommaso, C.M. Tracy, Y.J. Woo, D.X. Zhao, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology

Foundation/American Heart Association Task Force on Practice Guidelines, Circulation. 127 (2013) e362–e425. doi:10.1161/CIR.0b013e3182742cf6.

[33] National Institute for Health and Care Excellence, Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease, Natl. Inst. Heal. Care Excell. (2013).

[34] M. V. Jelinek, D.R. Thompson, C. Ski, S. Bunker, M.J. Vale, 40 years of cardiac rehabilitation and secondary prevention in post-cardiac ischaemic patients. Are we still in the wilderness?, Int. J. Cardiol. 179 (2015) 153–159. doi:10.1016/j.ijcard.2014.10.154.