REVIEW ARTICLE

Effectiveness of Non-invasive Interventions in Managing Cardiovascular Disease Using Specific Biological Markers

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Abstract

Background: Lifestyle interventions consisting of diet, exercise, psychosocial support and stress management are a clinically effective alternative to the management of cardiovascular diseases that can be feasibly measured and monitored during treatment using various biological markers. **Methodology**: A thorough Pubmed search was conducted looking for the results of articles that treated cardiovascular disease patients of both sexes and all ages with lifestyle modification in which the effectiveness of lifestyle modification was measured by various biomarkers. **Results**: The final review was conducted on 11 journal articles that were found examining exercise, diet, psychosocial support and stress management in cardiovascular disease patients and showing a positive benefit of such an intervention and the effects on biomarkers as an alternative to traditional pharmacological treatment. The affected biomarkers found were percent diameter coronary artery stenosis, blood pressure, cholesterol, body weight and fat, heart rate, HbA1c, exercise capacity, C reactive protein, triglycerides and BMI. **Conclusion**: Lifestyle modification consisting of exercise, low fat, high complex carbohydrate diet, psychosocial support and stress management is clinically efficacious in the treatment of cardiovascular disease as seen by the various changes in biological measures.

Keywords

Introduction

Cardiovascular disease (CVD) is the most common cause of death both in the United States, as well as worldwide. It accounted for an estimated 17.9 million deaths in 2016, representing 31% of all world deaths, according to the World Health Organization (1). In the US alone, health care spending and lost productivity from CVD exceeded $400 billion in 2006 (2). CVD includes coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. CVD risk factors are numerous, exposing potential areas for intervention, which include smoking, obesity, insulin resistance, physical inactivity, unhealthy diet, hostile personality and excessive use of alcohol. These risk factors are especially

pronounced in the lower socioeconomic demographic.

Standard Cardiac rehabilitation participation in America appears to be meager in the management of disease in the country. Estimates of participation rates in cardiac rehabilitation in the United States range from only 20% to 30% (3). Originally, post myocardial infarction care consisted of bed rest and immobility, and rehabilitation started to include early mobilization in the 1950s (4). The current consensus for cardiac rehabilitation now also includes dietary management in addition to health education. Adding to that, psychosocial support and stress management has also shown to be useful in recent years (5-11).

A so-called lifestyle intervention as cardiac rehabilitation targets specific risk factors of cardiovascular disease, in a way that is adapted into a healthy lifestyle for the remainder of a person's life, instead of a short-term exercise therapy and diet intervention. One of the first publications on such an intervention came from Dean Ornish over 25 years ago (5-6). He published the results of an intervention that not only alleviated the symptoms of cardiac disease, but also decreased the diameter of coronary artery stenosis in the absence of invasive therapy. Such findings were remarkable, and whether they have made a profound impact on the health care system will be explored in this paper.

Aims & Objectives

It is the purpose of this article to examine the effects of lifestyle interventions in the absence of pharmacotherapy and invasive procedures and identify bio-physiologic markers that can be used monitor the reversal of disease through a proper diet, exercise and psychosocial support as expressed by changes in biomarkers. It will be further explored how this type of intervention affects different demographics, patients with different severity and comorbidities of the disease.

Material & Methods

Pubmed was the central database searched. Keywords/MeshTerms included: Atherosclerosis, Coronary artery disease, exercise, diet fat-restricted, humans, lifestyle, quality of life, risk factors, social support, body mass index, peripheral arterial disease/rehabilitation. All ages and sexes were included. A search for original articles published between 1995 and 2016 and focusing on atherosclerosis regression, cost-effectiveness, lifestyle modifications including RCTs, cohort studies, multicenter studies and case control studies and only in the English language. Exclusions were foreign language articles, non-human studies and papers published before 1995. Only RCT, multi-center trials, cohort and case control studies were included in this review study.

Results

Overall, 11 journal articles were analyzed in this paper. While 9 papers primarily focused on lifestyle interventions including exercise, psychosocial aspects and diet in cardiovascular disease patients, two studies further explored gender, two studies looked at different socioeconomic demographics and finally, five studies looked at comorbidities and varying degrees of disease to further stratify research findings.

The types of study designs are outlined in Table 1.

Table 1. Summary of study designs	
Study design	Number of studies
Randomized Controlled Trial	6
Cohort	1
Prospective time series	2
Case-control	1
Stage IV Trial	1

All papers measured a variety of biological and psychosocial parameters with lipid profiles, exercise capacity, diet adherence, BMI, percent coronary artery stenosis and blood pressure being the most common, which are further explored in this study. The evidence table for the selected articles can be viewed in the appendix (Table 2).

The Multisite Cardiac Lifestyle Intervention Program

Six of the studies were based on the Multisite Cardiac Lifestyle Intervention Program (MCLIP) (7-13), the efficacy of which has been previously established in phase III randomized clinical trials (5-6, 14). The intervention consisted of these components; diet, exercise, smoking cessation and psychosocial support. The diet consisted of a low fat, plant-based diet, high in complex carbohydrates. 10% daily calories were derived from fat, 15% from protein and 75% from complex carbohydrates. Patients were responsible for their own meal preparations. Exercise was the second component, which included a minimum of 3 hour per week of aerobic exercise at 45% - 80% of predetermined maximal heart rate, as well as strength training two times a week. The last aspect of the lifestyle intervention program consisted of psychosocial behavior modification. This

included stress management with gentle yoga poses, progressive muscle relaxation, breathing exercises, meditation, guided imagery, as well as group support sessions to provide social support and maintain program adherence. The results of these studies will be subsequently described.

Efficacy of lifestyle changes in patients with a left ventricular ejection fraction of ≤40%

The majority of studies in this field have studied patients with moderate cardiovascular disease. In a 2007 study by Pischke *et al.* (12), researchers determined that patients with an angiographically determined left ventricular ejection fraction (LVEF) of less than or equal to 40% achieved similar medical and psychosocial benefits as cardiovascular disease patients with an ejection fraction of over 40% (n= 440, $p < 0.05$). Regardless of LVEF, all participants showed a reduction in weight, body fat, systolic and diastolic blood pressures, resting heart rate, total cholesterol, LDL-C, and an increase in exercise capacity (measured in metabolic equivalents, METs) at 3 months when compared to baseline and most parameters such as body weight improvements, diastolic blood pressure, total cholesterol, LDL-C and exercise were maintained over 1 year.

Micro and macrovascular endothelial function

Obesity is a well-documented risk factor for atherosclerosis, which begins with endothelial dysfunction. A study published by Bruyndonckx *et al.* (15), measured the micro and macrovascular effects of a lifestyle change in obese adolescents (n = 61). This study administered 2 hours per day of supervised play and physical activity, 2 hours a week of physical education at school, as well as 3 sessions a week of 40 minutes of supervised training sessions by qualified physiotherapists. Diet was restricted to 1500 – 1800 kcal/day and psychological support was also provided. Obese adolescents on the waiting list for the intervention were used as controls, which were managed by their regular physicians, focusing on caloric restriction and encouragement to exercise. Macrovascular endothelial function was tested by assessing brachial artery response using flow-mediated dilation. Microvascular endothelial function was measured in three ways: (1) using an Endo-PAT device which uses pneumatic probes positioned on the index fingers to measure changes in finger arterial tone, (2) measurement of circulating endothelial progenitor cells (EPCs), which are important contributors to endothelial repair, (3) measurement of endothelial microparticles (EMPs)

which are released from activated and apoptotic cells during endothelial dysfunction. The study found a significant increase in EPCs at five months ($p = .01$), as well as a statistically significant reduction of EMPs ($p = .004$) and an increase in peak arteriolar response ($p = .04$) at completion (10 months) of the study. Other significant findings included weight loss, decreased body fat percentage, lowered LDL cholesterol, increased HDL cholesterol, decreased C-reactive protein, and an increased exercise capacity (all $p < .05$).

Exercise on peripheral arterial disease (PAD)

Peripheral arterial disease can be a cause of decreased mobility in patients, which in turn not only limits their quality of life, but also contributes to further disease progression. A study by Gardner *et al.* (16) showed that symptomatic patients with peripheral arterial disease can not only increase the time of onset of claudication during physical activity, but they also showed improved microcirculation in patients that walked 3 times a week at a self-selected pace and participated in light resistance training in the setting of their own homes (n = 180). Experimental participants received roughly 1 hour of interaction with the research staff over the course of the three-month study, testing the efficacy of self-administered programs. Interestingly, they found that the home exercise group performed more exercise than their supervised exercise counterparts ($p < .001$), decreased C reactive protein ($p < .015$) a marker of inflammation, and saw an improvement in large artery elasticity index ($p < .006$). The 6-minute walk distance test was increased for both the experimental group as well as the supervised exercise group, but not for the usual care group. Adherence rates for the home exercise group were similar to the adherence rate of the supervised exercise group, and a conclusion was made that individualized monthly feedback was sufficient for patient adherence.

Lifestyle interventions in different socioeconomic groups

Cardiovascular disease risk factors such as smoking, hypertension, diabetes, physical inactivity, dyslipidemia, hostility and depression are especially prevalent among patients of lower socioeconomic statuses (SES). Resource accessibility is scarce in those groups due to economic hardships, and it is not clear whether lifestyle changes are feasible and effective methods in the treatment of CVD in such populations. One study based on the MCLIP found

that while both participants of high and low SES (defined by education and income) improved in reducing dietary fat, increasing stress management, increasing exercise time and capacity, the lower SES group showed better results in dietary fat intake, hours per week of exercise and stress management than the high SES group at the end of the three months intervention (p < .05) (9). This resulted in improvements in weight, systolic blood pressure, HbA1c in diabetics, total cholesterol, triglycerides, LDL cholesterol, depression, perceived stress, hostility and quality of life (all p <0.05).

Another study done in the United Kingdom published its results on home based vs. center-based rehabilitation in a socioeconomically deprived population (n = 525) and found that home-based treatment with exercise, relaxation, education and lifestyle counselling was not inferior to center based rehabilitation (p < .05), however, unfortunately their intervention was also not less costly (17). While the study did have multifactorial non-adherence rates of 9% they found that even those who did not adhere to the full program still made some positive lifestyle changes. Positive improvements were measured by changes in total cholesterol.

Gender trends

While examining SES trends at baseline in the study by Govil *et al*. (9), researchers found that regardless of SES, women were more likely to have a worse baseline profile when compared to men. Women had higher BMIs, exercised less, had a lower exercise capacity, a lower physical quality of life, and were less likely to be married. While previous studies have shown that more intensive lifestyle changes produced better results, they were accompanied by lower participation rates, especially among women (18-19). Toobert *et al*. (20) explored the possibilities of using moderate intensity lifestyle interventions with a particular focus on program adherence and long-term maintenance in postmenopausal diabetic women at high risk for CHD through either a tailored social support program through community resources or through a lay lead support group (n = 279). They found that while both methods were effective, the lay lead support groups appeared to be more effective in maintaining long term lifestyle changes, even after two years (p value not reported).

Lifestyle changes in patients with Diabetes Mellitus (DM)

Whether CVD changes could be attained in a similar manner in diabetic patients vs. non-diabetic

patients, was explored in a study by Pischke *et al*. (n = 440)(10). Following the MCLIP, the researchers found that at baseline the BMI, body weight, systolic blood pressure and heart rate in men with DM was significantly worse than in the non-diabetic control group. Women with DM had increased weight, and lower exercise capacity (measured in metabolic equivalents, METs) than men with DM. Plasma lipids were similar in diabetics vs non-diabetics. Both sexes with DM reported lower quality of life and exercised significantly less. Regardless of sex or DM status, all participants showed decreased weight and fat, lowered heart rates and LDL cholesterol, and increased their exercise capacity. These changes were seen at three months and maintained at one year (all p<0.05). Additionally, all patients had improved their diets, exercising and stress management. This showed that both patients with and without DM could clinically benefit from lifestyle changes to reduce their cardiovascular disease risk factors and improve health.

As mentioned in the previous section, the study conducted by Toobert *et al*., also showed favorable outcomes in CVD risk factors in postmenopausal women with diabetes, even though the study did not have a control group for postmenopausal women without diabetes (20).

Effectiveness

Two studies based on the MCLIP talked about the effectiveness of the intervention based on long term adherence, and external validity. Ornish *et al*. found that percent diameter stenosis of coronary arteries decreased from baseline in experimental participants, whereas increased in the control group after 1year (p = .02) and further after 5 years (p = .001) of the intervention (n = 35)(7). This relationship was not related to age or disease severity, but was related to program adherence, showing that positive changes can be obtained within a variety of patient variables. Adverse cardiac events were also less numerous in the experimental group during that time.

External validity was observed in another study, also within the MCLIP. Silberman *et al*., evaluated the effectiveness and efficacy of the intensive cardiac rehabilitation program in 24 different sites in America (in four different states) with a sample size of 2974 people (8). Positive improvements were seen in all tested biomarkers such as lipid profile, hemoglobin A1c in those who were diabetic, blood pressure, BMI, exercise, hostility and depression,

except for HDL which was decreased, although not as much as LDL (p < .005 for all measures), however the prognostic significance of low HDL with a healthy diet versus a typical American diet has been reported to be conflicting and unclear.

Relative contribution of health behaviors

In the multicomponent lifestyle intervention, Daubenmier *et al*. set out to determine the relative contribution of the different intervention components to the health changes observed with the MCLIP (n = 869) (13). They found that stress management and low dietary fat intake were additively related to weight loss (p < .01 and p < .001, respectively). Decrease in total cholesterol was predicted by reduced dietary fat intake (p < .001), as well as by exercise in women (p < .05), but not in men (p = .27). Increased stress management was also related to a decrease in triglyceride levels, HbA1c in diabetics and hostility (all p < .05). In conclusion, the authors found that diet changes, exercise and stress management are "individually, additively and interactively related to improvements in multiple coronary risk and psychosocial factors" (13).

Another study compared a diet and exercise control group to a diet, exercise and stress reduction intervention group in hypertensive patients (n = 113)(11). The stress management intervention consisted of weekly one-hour sessions of yoga, qigong, breathing and meditation sessions as well as weekly group support counselling meetings focusing on stress management. They were also given a 10-minute qigong guided imagery audio CD for daily home use. The study found that not only did the experimental group have better adherence rates (70% in experimental group and 30% in control group) but they also found that more patients in the experimental group reduced their blood pressure medications (p = .006), had a better outcome in their cholesterol profiles (p=.0001), and reported better quality of life in physical, mental and total scores, as calculated by the Short Form 36 Health Survey (SF36).

Discussion

The data presented in the results section has been consistent with the notion that a multi-intervention lifestyle consisting of stress management, diet and exercise can be used to supplement and, according to some papers, replace traditional pharmacotherapy in patients with cardiovascular disease. This has important clinical significance due to the fact that this intervention has little to no adverse side effects when compared to pharmacotherapy and surgical interventions and is more efficacious than standard cardiac rehabilitation. Additionally, it also provides the patient with an internal locus of control in regards to their health and its management, has a potential of decreasing long term health costs for the patients, especially when compared to standard drug treatment, and has consistently shown to increase the physical quality of life for most participants. The studies have also shed light on to the different ways that a cardiac lifestyle intervention can change a broad variety of biomarkers that can be used to track the progress of the intervention. Weight, lipid and cholesterol profiles, exercise capacity, blood pressure, and CRP were the most frequent biomarkers reported with an improvement after intervention. Additional biomarkers showing favorable results include heart rate, micro and macrovascular function, HbA1c s well as large artery elastic index.

Participation

According to a 2015 study by Doll *et al*, the researchers found that only about 60% of cardiac patients were referred to a standard cardiac rehabilitation program, and only one third of those attended at least one session in the same year (21). If that is compared to the lifestyle cardiac intervention programs, it becomes evident that there is a large problem in America when it comes to participation. Another study found that being female, older and having diabetes lessens the chance that a patient will participate in a cardiac rehabilitation program, shedding light to the population demographic which should be better targeted (22). Other studies found the common reasons of non-participation to be high copayments, time requirements of certain programs, or because of no physician referral. Knowing that certain biomarkers are available to track progress of a person undergoing the intervention, clinicians may one day use these changes to approximate program adherence and further manage the patient accordingly.

The Multisite Cardiac Lifestyle Intervention Program and others

The Multisite Cardiac Lifestyle Intervention Program (MCLIP) has been proven to be efficacious not only in halting progression, but also in the reversal of coronary heart disease, as measured by angiography

as well as numerous biomarkers. While angiography is an accurate way to assess disease progression, it is invasive and is not recommended for repeated testing. In this case, other biomarkers are useful during the intervention to monitor the disease. The biomarkers found in this study that reflected positive change in disease include percent body fat, weight, blood pressure, heart rate, cholesterol, triglycerides, and exercise capacity. Remarkably, results were seen as soon as after three months, and were continued to be seen after five years in the studies that assessed the MCLIP. This program is currently provided in only 18 of the 50 states, and as of 2010, is covered by Medicare under Intensive Cardiac Rehabilitation (ICR). There are only two other similar programs that are provided under ICR: the Pritikin program (Miami location) and the Benson-Henry Institute Cardiac Wellness Program (Boston location). These programs not only pose a problem of accessibility, but also that of cost. For example, for patients not covered by the Medicare program, a two weeks retreat to the Pritikin longevity center can cost more than $6,000 USD (www.Pritikin.com).

Efficacy of lifestyle changes in patients with a left ventricular ejection fraction of ≤40%

While exercise, stress management and a good diet has a potential to be of use to healthy people as well as those with CVD, it was shown by Pischke *et al*. to be beneficial even in patients with severe CVD, such as those with congestive heart failure (CHF), as defined by an ejection fraction of less than or equal to 40% (12). This has tremendous implications as this population is more aggressively managed with medications that have high adverse effect profiles and have worse baseline measurements of biomarkers when compared to patients with an EF of >40% and therefore have the potential for increased improvement in their health through a relatively safe cardiac lifestyle intervention. Moreover, the same study found that the intervention was so effective that some patients needed to decrease medication dose or stop certain medications altogether. Dunlay *et al*. have found that patients with an ST elevation MI or receipt of reperfusion therapy had higher rates of cardiac rehab participation, showing that patients with a more serious course of CVD may be more likely to participate in cardiac rehabilitation (22). For these patients, regular checks for changes in blood pressure, heart rate, total cholesterol and LDL-C can be a very useful way to monitor disease changes.

Micro and macrovascular endothelial function

Endothelial dysfunction is a well-known precursor to vascular disease, if endothelial health can be preserved through the lifestyle intervention, it makes sense to conclude that it would slow down or halt the progression of CVD, and possibly repair already damaged vessels, as was discovered by Bruyndonckx *et al*. (15). The techniques used in that particular study could be beneficial in treatment monitoring as well as to identify populations at risk. Increase in endothelial precursor cells is a sign of vascular repair, while decrease in endothelial microparticles is a biological clue that vascular damage may have decreased.

Exercise on peripheral arterial disease (PAD)

Gardner *et al*. discovered that regular exercise alone can increase time to onset of claudication, showing improvement in peripheral vascular disease, a disease that is part of the spectrum of CVD (16). Along with other research, this shows that lifestyle interventions can alleviate disease severity not only when it comes to coronary heart disease as shown by Ornish *et al*., but also in other areas of the body (7).

Gender and SES trends

As was previously described in multiple studies, women, especially of the lower SES had worse baseline measures than men. Since for women, heart disease is also the leading cause of death, targeting women through this intervention should be one of its priorities.

Making this treatment accessible to the lower SES demographics is also a pertinent issue. Cost, accessibility as well as feasibility is generally an issue in this population. Can all patients receive insurance coverage for this program? Can a single mother working multiple jobs have time for exercise, proper diet and stress management? It is difficult to conduct truly valid studies to assess this because every patient's situation is unique, however Govil *et al*. and Jolly *et al*. were able to approximate the effectiveness of the lifestyle intervention problem in such demographics and show that while it may be difficult, theoretically, it is possible (9, 17). Silberman *et al*. has shown that the common misconception regarding the feasibility of the intervention is not necessarily true, and while it may be a challenge to many patients, the adherence rates are relatively good, especially when compared to controls (8). A positive influencing factor may be the psychosocial support that the participants receive in the program, even when the support groups were lead by a lay

person (vs. personalized professional support) (20). Simple regular measurements of heart rate, blood pressure, weight change and percent body fat are relatively less expensive than other biological measurements, and can be easily used to monitor the intervention progress without the additional fees for more invasive procedures.

Lifestyle changes in patients with Diabetes Mellitus (DM)

Diabetic patients were also found to benefit and to better manage their disease, as seen with improved HbA1c. This demographic was also reported to have a decrease in weight, body fat, heart rate, LDL and cholesterol. A 2014 report by the Center for Disease Control and Prevention (CDC) has estimated that in 2012, a total of 29.1 million Americans had the disease and the estimated total medical cost of disease was $245 billion dollars, making this topic extremely relevant (23). This demographic of cardiac patients is an important target as they have also been found to be less likely to participate in Cardiac rehabilitation programs (24).

Relative contribution of health behaviors

While one paper used only exercise as their intervention, the rest of the studies have shown that in general more impressive results can be seen when a combination of interventions are used. The interventions are closely connected with each other in the complex way that they contribute to the improvement of CVD. Since different combinations of interventions affected different biomarkers, as has been described in the results section, it is possible to use those combinations to monitor disease progression in those patients that cannot partake in the entire program due to health restrictions, or other personal constraints.

Insurance and nonadherence

While the efficacy has been clearly demonstrated in the MCLIP, its feasibility poses certain problems, primarily that of financing. In the MCLIP, most of the participants had their program costs covered by their insurance plans, yet some people had to pay out of pocket. Is there a way to create a program like this that is universally accessible? Staying in sync with current technology, perhaps the program can be made better through applications for smartphones that are created by physicians to accompany the program for patients who cannot afford the entire program or have other accessibility issues. Nowadays smartphones can track parameters such as heart rate, daily distance walked and BMI which

can be used by the patient in the absence of medical supervision as feedback about their progress within the intervention.

Jolly *et al*. found that some non-adherence issues were related to other comorbidities such as arthritis, which limited the patients ability to participate (17). Such a problem could potentially be solved by changing the fitness program, for example, to a modified aqua fitness session, especially designed for cardiac rehabilitation. To prevent the program from being monotone and increasing adherence, the program could be modified to take advantage of local resources, such as hikes, swimming, skiing, skating, whatever the area and community offers during the different seasons.

Shortcomings of the lifestyle intervention

While the results that were attained by the patients with strong adherence are very encouraging, all studies had a non-adherence rate of at least 5% or more. Some of the reasons were other comorbidities such as pain due to arthritis, difficulty of program, adverse incidents, change in insurance providers that no longer covered intervention and low social support (17, 15, 7-8, 12, 9). It remains to be explored whether regular monitoring of the biomarkers found associated, with the lifestyle intervention treatment can help motivate patients and adhere to the program, as most of the biomarkers can be easily attained in a relatively noninvasive manner.

Future Perspectives

Accessibility, physician referral, insurance coverage are all issues that need to be addressed if cardiac patients are to participate in the lifestyle cardiac rehabilitation program on a larger scale, and for heart disease rates and health costs to be attenuated. Now that this article has identified key biomarker changes that play a significant role during the intervention, it would be of interest to discover how else these biomarkers can be used to make the intervention even more effective.

Conclusion

Lifestyle interventions as treatment for cardiovascular disease have been gaining popularity in the past two decades. Changes in the following biological measures have been identified in this paper: decrease in weight, fat, total cholesterol, LDL, blood pressure, heart rate, HbA1c, endothelial microparticles, C reactive protein, percent diameter stenosis of coronary arteries, BMI, hostility, depression, and triglycerides. An increase was found

in exercise capacity, endothelial precursor cells, peak arteriolar response, large artery elasticity index, 6 minute walk distance and quality of life. Other biological measures should be explored to further the treatment of cardiovascular disease.

Considering the strong scientific evidence showing the clinical efficiency in the treatment of the disease, as well as evidence in the improvement of the physical quality of life, this is an area that needs greater attention from healthcare providers, law makers as well as insurance companies.

Recommendation

Based on the evidence presented in this article, it is possible for physicians to commonly use the recommendation for patients to engage in self-monitoring of health benefit progression through easily obtainable biomarkers at home, while simultaneously using laboratory obtained lab markers in the office to track progress.

Limitation of the study

This study excluded articles published in foreign languages as well as studies published prior to 1995 which could have excluded clinically relevant articles from analysis.

Relevance of the study

Empowerment of patients through the knowledge that they can specifically track their cardiovascular health through simple as well as laboratory biomarkers has the potential to alter the trend of increasing cardiovascular death rates in the future. Patients need to be reminded by physicians, that no matter how advanced their cardiovascular disease may be, it is possible to stop progression or even stimulate regression.

Authors Contribution

Both the authors contributed to this study.

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Tables

TABLE 2 EVIDENCE TABLE

Author	Date of publication	Study Design	Level of Evidence	Study Population	Therapy or Exposure	Outcome/result
1. Ornish *et al*.	Dec 1998	RCT	1	48 patients with moderate to severe coronary heart disease	Intensive lifestyle changes for 5 years (10% fat whole foods vegetarian diet, aerobic exercise, stress management, smoking cessation, group psychosocial support)	Experimental group experienced a decrease in the average percent coronary stenosis whereas the control group experienced continued atherosclerosis and more than twice as many cardiac events
2.Silberman *et al*.	March 2010	Multicenter Study	3	2974 subjects from 24 socioeconomically diverse sites	Subjects participated in an intensive cardiac rehabilitation program	Improvements in BMI, TG, total cholesterol, HbA1c, SBP, DBP, depression, hostility, exercise and functional capacity which were maintained after 1 year. Program showed to be feasible
3. Govil *et al*.	July 2009	Prospective cohort	3	869 low vs high SES predominantly white non-smoking CHD patients in the insurance-sponsored Multisite Cardiac Lifestyle Intervention Program	Lifestyle change program: 2 times a week for 3 months (104 hours) individualized nurse case management, interactive lectures, demonstration, supervised exercise, 1 hour group support	Less educated (low SES) patients showed improvements in self-reported diet management, exercise, and stress management. Results were accompanied in improvements in weight, BP, LDL, and exercise capacity.
4. Pischke *et al*.	May 2006	Controlled clinical trial	2	440 nonsmoking patients with CAD and with or without DM	Plant based low fat diet, exercise, stress management for 1 year in CAD patients with and without DM	DM patients demonstrated comparative improvements in weight, LDL, exercise capacity and quality of life. 19.8% diabetic patients decreased medication.
5. Ziv *et al*.	2013	RCT	1	113 hypertensive men and women	Exercise 45 min walk 4 times per week, whole grain rice, low fat diet, stress management through yoga, qigong and weekly group support	Decreased BP, decreased medication use, decreased cholesterol, increased physical and mental life quality.
6. Pischke CR., *et al*	May 2007	Non-randomized control trial	2	CHD non-smoking patients with =/<40% and >40% LVEF	Multicenter Lifestyle Demonstration Project (low-fat, plant based diet; exercise; stress management)	CHD patients with =/<40% LVEF achieved similar medical and psychosocial benefits as patients with LVEF >40%

7. Daubenmier *et al*.	2007	Cohort	4	869 nonsmoking CHD patients	Low fat, high complex carb diet, 3h/week exercise, stress management, support groups	Increased stress management: decreased HbA1c, hostility, decreased TG. Exercise decreased total cholesterol in women. Diet + stress management reduced weight.
8. Bruyndonckx L., *et al*	March 2015	RCT	1	Obese adolescents 12-18 years	Exercise and supervised diet vs ambulant treatment	Treatment regimen decreased endothelial dysfunction and improved other obesity related factors
9. Gardner *et al*	Sept 2014	RCT	1	180 patients randomized to 3 groups: a home exercise program, a supervised exercise program and an attention control group	walking to mild - moderate claudication pain for 12 weeks, controls performed light resistance training	Home exercise utilizing minimal staff supervision has low attrition, high adherence, and improves claudication onset time, peak walking time, submaximal exercise performance, daily ambulatory activity, vascular function, inflammation and calf muscle Hb oxygen saturation
10. Jolly *et al*.	2007	RCT	1	525 patients who have had an MI or revascularization in the last 12 weeks	Exercise, education, relaxation, lifestyle counselling,	Adherence was maintained with minimal contact from staff. Cost difference of home treatment and center based was insignificant. Nonadherence reasons were multifactorial
11.Toobert *et al*.	2002	RCT	1	279 Postmenopausal women with diabetes at high risk for CHD	3-day retreat and weekly lessons for lifestyle modification. Mediterranean diet, 3h per week exercise. Stress management: 20 min yoga, 15 min progressive muscle relaxation, 15 min meditation, 5 min imagery.	Better long term program adherence in lay-led groups. Dietary, stress management, and physical activity changes made by intervention women were significant and lasting. Improvements in body mass, angina symptoms, quality of life and reduction of blood pressure lowering medications was observed