Contemporary Clinical Trials 79 (2019) 37–43

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

PCI Alternative Using Sustained Exercise (PAUSE): Rationale and trial design

Jonathan Myers*, Holly Fonda, Minal Vasanawala, Kieran Chung, George Segall, Khin Chan, Patricia Nguyen

Veterans Affairs Palo Alto Health Care System, Division of Cardiovascular Medicine, Stanford University, United States of America

ARTICLE INFO

Keywords:
Cardiac rehabilitation
Exercise
Exercise testing
Percutaneous coronary intervention
Coronary artery disease
Cost-effectiveness

ABSTRACT

Cardiovascular disease (CVD) currently claims nearly one million lives yearly in the US, accounting for nearly 40% of all deaths. Coronary artery disease (CAD) accounts for the largest number of these deaths. While efforts aimed at treating CAD in recent decades have concentrated on surgical and catheter-based interventions, limited resources have been directed toward prevention and rehabilitation. CAD is commonly treated using percutaneous coronary intervention (PCI), and this treatment has increased exponentially since its adoption over three decades ago. Recent questions have been raised regarding the cost-effectiveness of PCI, the extent to which PCI is overused, and whether selected patients may benefit from optimal medical therapy in lieu of PCI. One alternative therapy that has been shown to improve outcomes in CAD is exercise therapy; exercise programs have been shown to have numerous physiological benefits, and a growing number of studies have demonstrated reductions in mortality. Given the high volume of PCI, its high cost, its lack of effect on survival and the potential for alternative treatments including exercise, the current study is termed "**P**CI **A**lternative **U**sing **S**ustained **E**xercise" (PAUSE). The primary aim of PAUSE is to determine whether patients randomized to exercise and lifestyle intervention have greater improvement in coronary function and anatomy compared to those randomized to PCI. Coronary function and anatomy is determined using positron emission tomography combined with computed tomographic angiography (PET/CTA). Our objective is to demonstrate the utility of a non-invasive technology to document the efficacy of exercise as an alternative treatment strategy to PCI.

1. Background and rationale

Cardiovascular disease remains the most common cause of death throughout the Western World. This condition currently claims nearly one million lives yearly in the US, accounting for approximately 40% of all deaths [1]. The total cost of cardiovascular disease in the US, including hospitalizations and lost productivity, was approximately $555 billion in 2016 [2]. Coronary artery disease (CAD) accounts for the largest number of deaths and the majority of these costs.

Since its inception more than three decades ago, the use of percutaneous coronary intervention (PCI) has become the most common procedure for the treatment of CAD, and its use has increased considerably. There are > 1.3 million stent procedures performed in the US yearly [1], accounting for roughly 10% of the overall increase in Medicare expenditures [3]. Evidence suggests that the rate of increase in PCIs has leveled off in recent years, but the cost of PCI remains substantial, estimated to be $67,000 per procedure [1].

In light of the extraordinary increase in the use of PCI in recent years, questions have been raised regarding its cost-effectiveness, the extent to which PCI is overused, and whether selected patients may benefit from optimal medical therapy (OMT) in lieu of PCI [5–9]. In the recent ORBITA trial for example, no differences in exercise capacity were observed between 200 patients randomized to PCI or a sham procedure after 6 weeks [4]. Despite the fact that PCI is expensive, repeat PCI is common [10], and there is no evidence for improved survival [11], alternative therapies are rarely considered. While efforts aimed at treating CAD have concentrated on surgical and catheter-based interventions, limited resources have been directed toward prevention and rehabilitation [12–14]. One alternative therapy that has been shown to improve outcomes in PCI candidates is intensive lifestyle

* Corresponding author at: VA Palo Alto Health Care System, Cardiology 111C, 3801 Miranda Ave, Palo Alto, CA 94304, United States of America.
E-mail address: drj993@aol.com (J. Myers).

https://doi.org/10.1016/j.cct.2019.02.010
Received 29 November 2018; Received in revised form 9 February 2019; Accepted 19 February 2019
Available online 20 February 2019
1551-7144/ Published by Elsevier Inc.

intervention, including exercise training. Although there have been a number of comparisons between OMT and PCI OMT has rarely included exercise intervention, and little is known regarding the effects of exercise intervention on myocardial perfusion as an alternative to PCI.

Regular exercise has been shown to be an effective therapy for a multitude of chronic conditions. Many recent studies have not only shown protective effects of regular exercise for a wide spectrum of disease processes [12–15], but have also demonstrated cardiorespiratory fitness (CRF) to be a more powerful independent predictor of all-cause mortality than traditional risk factors in various clinical populations [12,16–19]. The evidence supporting the prognostic applications of CRF was the impetus behind a recent AHA Scientific Statement advocating the routine assessment of CRF as a clinical vital sign [19]. Given the high volume of PCI, its high cost, its lack of effect on survival and the potential for alternative treatments including exercise and risk reduction, we initiated the trial termed "**P**CI **A**lternative **U**sing **S**ustained **E**xercise" (PAUSE). The primary aim of PAUSE is to employ non-invasive methods to determine whether patients randomized to exercise intervention have similar or greater improvement in coronary function and anatomy compared to those randomized to PCI.

2. Research design and methods

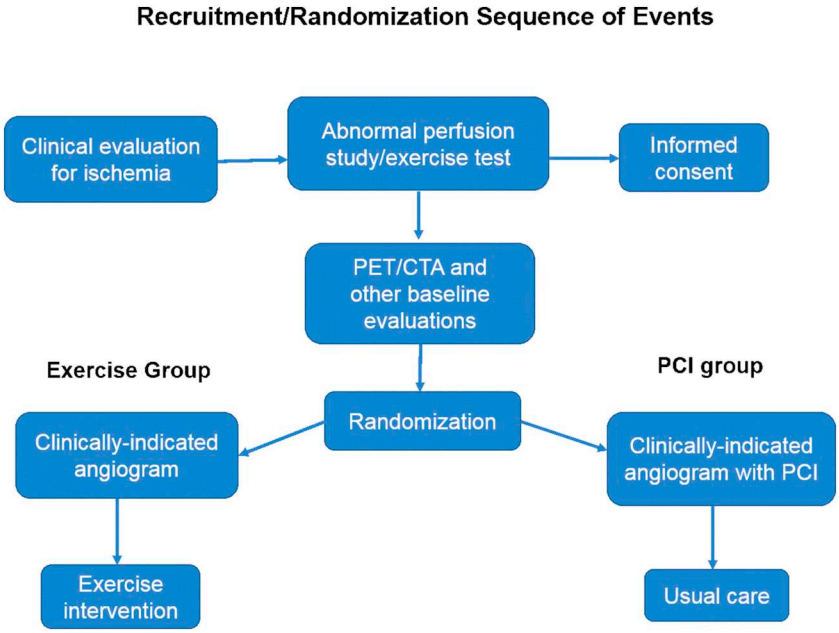
2.1. Study population

Stable patients between the ages of 50 and 70 years who have lesions appropriate for PCI based on American Heart Association/American College of Cardiology (AHA/ACC) criteria are considered for the study. Only patients with a good prognosis (annual mortality < 2% based on VA multivariate scores [20,21]) are considered. Patients with left main disease or proximal LAD disease are excluded.

2.2. Recruitment

Only subjects who receive their primary care at the VA Palo Alto Health Care System are considered for the study. Subjects are recruited from the following populations: 1) patients referred for a clinically-indicated stress myocardial perfusion study; and 2) patients who have anginal symptoms and/or a positive exercise test with > 1.0 mm ST-segment deviation from baseline on a standard treadmill exercise test, estimated to have > 80% probability of disease based on VA scores [20,21]. Only those patients who would normally undergo coronary angiography for clinical reasons are potential participants in the study. Patients with significant left main disease, proximal LAD disease, and those with diabetes mellitus or 3 vessel disease are excluded. Subjects who agree to participate are consented, and then undergo baseline testing, including cardiopulmonary exercise testing, symptom and quality of life questionnaires, and PET/CTA. They are then randomized to either the exercise or usual care groups. A clinically-indicated angiogram is then performed, and subjects randomized to the PCI group undergo PCI.

The sequence of events for recruitment and randomization is as follows:



A total of 64 subjects are being actively recruited; randomization is stratified by age, exercise capacity, and BMI so that these variables will be matched evenly between exercise intervention and PCI groups.

After informed consent is obtained, participants undergo a standard clinical examination and thorough medical history. Along with the baseline exercise test, questionnaires are administered regarding current and past physical activity patterns, quality of life, and symptoms. Fasting blood labs are obtained on a different day than the exercise test.

2.3. Cardiopulmonary exercise testing

Peak VO_2 is determined at baseline and after 6 months and 1 year on a treadmill using an individualized ramp protocol with collection of continuous ventilatory gas exchange responses. In accordance with standard practice at the Palo Alto VAHCS, prior to exercise testing, patients complete a questionnaire to estimate exercise capacity; the questionnaire is used to individualize the exercise protocol, which allows most patients to reach maximal effort within the recommended range of 8 to 12 min [22]. We previously observed that this protocol provides the closest relation between measured and estimated metabolic equivalents (METs) [23]. A 12-lead electrocardiogram, heart rate, and blood pressure responses are monitored throughout the exercise test and recovery period. Ventilatory gas exchange measurements are obtained continuously at rest, throughout exercise, and during 5 min of recovery. All subjects are encouraged to give a maximal effort, and the Borg 6–20 scale is used to quantify subjective effort [24]. Standardized clinical indications for stopping are used. ST-segment depression is measured visually at the J junction, and slope is determined over the

following 60 ms and classified as upsloping, horizontal, or downsloping. Blood pressure is measured manually, and exercise capacity is measured directly using ventilatory gas exchange techniques. The exercise tests are performed, analyzed, and reported according to a standardized protocol and utilizing a computerized database [25].

The Duke Treadmill Score [26] and the VA Prognostic Score [20] are used to help estimate risk and assess suitability for exercise training. The AHA Guidelines on Exercise Testing [27] recommend that the Duke Score, which incorporates ischemic responses, symptoms, and exercise capacity, be used for all clinical exercise testing to stratify risk. The VA Prognostic Score was developed at the VA Palo Alto Health Care System and incorporates pre-and post-test responses that have been shown to powerfully estimate risk in Veterans referred for exercise testing [20]. Patients with evidence of significant coronary artery disease as determined by profound ischemic markers, ominous arrhythmias, resting ECGs that confound the recognition of ischemia (bundle branch block, > 1 mm ST depression, paced rhythm) are excluded. Patients with hemodynamic instability or inability to exercise, those with complicating illnesses, or questionable motivation to sustain prolonged training are also excluded.

2.4. Exercise training

Initially, all subjects undergo supervised exercise sessions 1–3 times weekly over a 2-month period. The purpose of these sessions is to familiarize the patients to their individualized training program, assess stability during exercise, ascertain that they understand their exercise prescription and how to use activity and heart rate logs, and to provide guidelines and education in terms of what is expected of them during the study. Subjects then exercise at home, and weekly phone calls are scheduled with an exercise physiologist to ensure stability and compliance, to review activity logs, and to modify the exercise prescription as appropriate. Guidelines for patient monitoring, safety, and prescription outlined by the AHA, American College of Sports Medicine (ACSM), and American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) are followed [27–29]. The exercise sessions include 5-minute warm-up and cool-down sessions prior to and following a combination of continuous aerobic (treadmill walking, cycle ergometry, arm ergometry, rowing, stair climbing) and resistance exercise. Exercise intensities are initially targeted to achieve 40–60% of heart rate reserve for a duration of 30–60 min, depending on the initial fitness of the individual. Progression of exercise intensity is individualized in accordance with established guidelines (ACSM, AACVPR [27–29]), with the goal to increase intensity and duration to 60 to 85% heart rate reserve and at least 45 min, respectively. All in-house sessions and activity surveillance is supervised by exercise physiologists certified by the ACSM [29].

2.5. Resistance training

During the initial supervised sessions, resistance exercise involves an introduction to a low resistance, high repetition regimen including upper and lower body major muscle groups under individualized supervision in accordance with established guidelines. Resistance exercises will include leg press, leg extension, leg flexion, chest press, shoulder press, row, and lat pull-down. During the first month of the study, subjects perform 12 to 15 repetitions at 70% of the 5-repitition maximum with a minimum 2-min rest period between sets. Subjects gradually increase to 2 sets of these exercises, with increasing resistance as tolerated throughout the study. Resistance training sessions are performed 3 times weekly. Resistance exercise is performed in accordance with established guidelines [30,31], including proper consideration of breathing techniques, mechanics, individualized resistance, range of motion, and progression. Subjects are given handheld weights and Thera-Bands (Thera-Band, Inc., Akron, Ohio) in accordance with their capabilities and instructed on their use at home based on their individualized prescription. At the baseline, 6 month, and 12 month evaluations, maximal isometric strength is measured using a hand-grip dynamometer.

2.6. Home exercise training

Subjects undergo detailed instructions on individualized exercise prescription, including how to monitor exercise intensity using heart rate and perceived exertion, and how to use heart rate, activity tracking devices, and pedometers. Cycle ergometers are provided for home use (Stamina 4600, Springfield, MO), but the subjects are encouraged to achieve an individualized, targeted exercise stimulus using walking and other available modes of exercise to achieve their goals. Exercise guidelines are similar to those of supervised sessions. Subjects in the exercise group also undergo education and encouragement to increase their daily activities. Patient-oriented educational materials provided by the AHA and CDC are distributed to all subjects in the exercise group.

2.7. Additional monitoring of daily activities

In addition to the formal training sessions, subjects are encouraged to increase their daily activities, including exercising at a moderate intensity (using their individualized exercise prescription) for a minimum of 45 min each day they do not exercise at the VA facility. Activity is documented by issuing a pedometer (Accusplit AE-180, San Jose, CA) and a Polar heart rate monitor (Polar Inc. Kempele, Finland). Subjects are given standardized logs to record heart rate responses during activity and steps at the end of each day.

2.8. Monitoring phone calls

For all subjects, follow-up phone calls are made weekly in order to monitor compliance, to complete the Veterans Exercise Testing Study (VETS) 7-day activity recall questionnaire, and address any clinical concerns. Energy costs of activities are estimated from the ACSM Compendium of Physical Activities [32]. Energy expenditure is expressed in terms of both kcal/week and MET/hours/week. A parallel goal is to achieve 2000 kcals/week of energy expenditure based on the VETS 7-Day Recall Questionnaire; this amount is the equivalent of approximately 45 min to 1 h of moderate activity most days of the week. This amount has been a benchmark in epidemiologic studies both in the VA and other populations, and has been shown to have a strong inverse relation with mortality and cardiac events [33–35].

2.9. Blood panels

Standard blood labs and lipid panels including total cholesterol, LDL, HDL, ApoB, lipoprotein(a), C-reactive protein, fasting glucose, and triglycerides are determined at baseline, 6 months, and at 1 year for both groups.

2.10. Questionnaires

During screening, at 6 months, and at 12 months, patients are given a VA Physical Activity Questionnaire (VAPAQ), a Seattle Angina Questionnaire (to assess symptom-related limitations and perceptions), and a Quality of Life Questionnaire (SF-36, providing an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index).

3. PET/CTA study protocol

3.1. Rationale for the use of PET/CTA

Our objective is to demonstrate that exercise training, an intervention that improves coronary artery endothelial function, can improve

myocardial perfusion to a degree that is similar to PCI, an intervention that decreases localized vessel obstruction. Both interventions improve myocardial perfusion, but they have not been previously compared using this technology. Myocardial blood flow determined by PET will be the primary outcome measure. It will be measured by the sum difference score (SDS), which is defined as the difference between perfusion at stress minus rest. SDS provides information on myocardial perfusion pattern, highlighting the functional significance of anatomic stenoses. It is a well-validated, semi-quantitative measure of ischemia. It has been shown to be a precise correlate of the degree of coronary artery disease, with a predictive accuracy that that is superior to other non-invasive techniques including myocardial perfusion reserve [36]. Quantification of the SDS can be performed with chemical, exercise, or psychological stress [36].

A global myocardial perfusion pattern measure is preferred because a regional method could miss the global improvement in myocardial blood flow associated with exercise training. PCI treats the target lesion; specifically, it lessens the obstruction of the stenotic epicardial artery, resulting in regional flow improvement reflected in global changes. Thus, the most equitable comparison is a measure of the overall myocardial perfusion pattern and not just perfusion of the territory supplied by the stenotic artery. In addition, we have chosen SDS because previous studies have shown improvements in myocardial perfusion pattern following either exercise training [37,38] or PCI [39], and this type of stress is more convenient and reliable than other stresses. Exercise training, with durations ranging from 4 weeks to 1 year, has been shown to improve coronary endothelial function measured by invasive angiography [40] and myocardial perfusion measured by PET [38]. The latter study was an evaluation of 118 patients who underwent PCI and were then randomized after PCI to an exercise training or usual care group; the investigators reported a 19% improvement in myocardial perfusion pattern after 6 months of exercise training. Similarly, among patients evaluated before and after receiving PCI, a 20% improvement in myocardial perfusion measured by PET was observed [39]. However, a randomized controlled trial to determine whether exercise or PCI provides greater improvement in myocardial perfusion has not been performed.

PET perfusion imaging has also been shown to be highly reproducible. In repeat studies of coronary blood flow and coronary flow reserve, the correlation coefficients have been shown to be 0.98 and 0.96, respectively, with inter- and intra-observer reliabilities of 0.97 [41]. The diagnostic accuracy of PET has been reported in many studies; a weighted summary of these studies shows an overall predictive accuracy of 0.90, higher than other non-invasive methods for detecting coronary artery disease [42].

CTA, commonly performed in conjunction with PET, is a secondary outcome. CTA complements PET in that it can non-invasively quantify anatomical progression of atherosclerotic disease by determining the amount of calcified plaque burden, which is quantified by the coronary artery calcium score (CAC) [43]. CAC has also been shown to be highly reproducible [43], is strongly correlated with angiographic coronary disease [44], and is a powerful predictor of cardiac events independent of other cardiovascular risk factors [45]. The combination of PET/CTA provides information that previously could only be obtained invasively using coronary flow wires and invasive x-ray angiography. This permits a non-invasive way to evaluate both functional and anatomical adaptations to exercise.

3.2. PET methods

A hybrid 64-row PET/CT scanner (GE Discovery VCT, General Electric, WI, USA) is used in the study. Images are acquired with simultaneous ECG gating (8 frames/cycle). Heart rate, arterial blood pressure, and 12-lead ECGs are recorded continuously throughout the evaluation. Heart rate and the arterial blood pressure obtained during the first 2 min of each dynamic image will be averaged and used to calculate the rate-pressure product as an index of cardiac work.

Measurement of myocardial blood flow is performed at baseline and 1-year in all subjects. Intravenous ^{13}NH3 is used as the flow tracer and serial imaging with PET is performed [46,47]. Measurements are performed at baseline, and after pharmacologic stress with dipyridamole [48]. A 20-minute transmission scan is acquired first for correction of photon attenuation [49]. After the first intravenous injection of ^{13}NH3 (15 to 20 mCi), resting serial transaxial images are acquired in a sequence consisting of 12 image frames of 10 s, 2 frames of 30 s, and 1 frame of 900 s. Forty-five minutes later, 0.56 mg/kg of dipyridamole IV will be infused over 4 min [48]. ^{13}NH3 (15 to 20 mCi) is injected 4 min after the end of the dipyridamole infusion, and serial images are recorded in the same sequence. Myocardial blood flow at rest and following dipyridamole infusion is expressed as ml flow/100 g/min. Myocardial perfusion reserve is calculated as the ratio of myocardial blood flow during stress (e.g. after dipyridamole) and myocardial blood flow at rest.

Semi-quantitative evaluation of the perfusion deficits is used to compute the sum stress score and sum rest score. Stress and rest images are divided according to the 17-segment model [50]. Perfusion in each segment is scored based on the following scale: 0 – Normal, 1 – Slight (equivocal), 2 – Moderate, 3 – Severe, and 4 – Absent. The sum rest and stress scores are computed individually. The SDS is calculated by subtracting the sum rest score (SRS) from the sum stress score (SSS) (e.g., SDS = SSS – SRS) and reflects the global ischemic burden. The score defines whether ischemia is present and the location and extent of the ischemia relative to the specific myocardial territory. The size of myocardial perfusion defects is expressed as percentage of the left ventricle. In general, defect extent is defined as small (5 to 10% of the left ventricle), medium (15 to 20% of the left ventricle), or large (> 20% of the left ventricle). Defect severity is defined as mild, moderate, or severe based on myocardial tracer content compared against normalized data [51]. Blinded, qualitative, consensus interpretation is performed by Drs. Nguyen, Vasanawala and Segall.

3.3. CT Imaging

After myocardial perfusion imaging, all patients undergo calcium scoring and CT angiography (120 kv; 500 mA). First, a prospectively gated low dose sequential CT scan of the heart is performed for coronary calcium detection and quantification. Patients with pre-scan heart rates above 70 beats per minute receive intravenous beta-blocker therapy (5 to 15 mg metoprolol tartrate) immediately prior to the CT scan if no contraindications are present. Additionally, 0.04 mg of sublingual nitroglycerin is administered for coronary dilatation prior to the scan. ECG-pulsing for radiation dose reduction is used in all patients. Synchronized to the ECG, CT data sets are retrospectively reconstructed in mid- to end-diastolic phases and additional phases if needed for optimal coronary artery visualization. Standard reconstruction parameters for slice thickness, field of view, and convolution kernel is used. For post-processing and image interpretation, the images are then transferred to an external designated workstation (Advantage Workstation, GE).

A comparison of coronary lesions (progression or regression of stenosis and change in calcified and noncalicified plaque area) between the two groups at baseline and 1 year post-randomization using CT with contrast is a secondary outcome. For analysis of anatomy [51], a scoring system is used to quantify disease progression or regression. Stenoses with < 10% change in diameter reduction will be classified as unchanged (± 0). A difference ≥ 10% between baseline and follow-up is graded as progression (+1) and a negative difference ≥ 10% is graded as regression (−1). Any lesion that necessitates intervention by PCI or bypass surgery is assigned a grade of +3. Progression from subtotal occlusion to total occlusion (99% to 100%) and spontaneous recanalization is not graded. In the culprit lesion, an asymptomatic in-stent restenosis < 50% is calculated as no change (± 0). An in-stent

restenosis of ≥50% is rated as progression (+1). An in-stent stenosis ≥50% that required intervention is classified as progression (+3). A single variable is calculated per patient by adding the grades assigned to the separate stenoses. For analysis of calcified and non-calcified plaque burden [52], the coronary arteries are divided into 12 segments according to the AHA classification [43]. For every coronary artery segment (identified via side branches) the presence of calcified or noncalcified plaque, both, or neither is determined using axial and multiplanar reformatted images. To measure plaque volume in each coronary segment, contiguous 1 mm thick cross sectional images of the coronary arteries are rendered and displayed with a fixed setting (700-HU window, 200-HU level). Plaque areas are manually traced and volume calculated by multiplying area and slice increment. In the distal segments, analysis of plaque is limited to the proximal 20 mm. For comparison of calcium scores, total calcium and per artery calcium scores is compared.

4. PCI group

The PCI group is followed by their cardiologist and receives usual clinical care. Subjects in both groups are Veterans who receive their routine care at our facility. The testing schedule, timelines, and all procedures (except exercise training and PCI) are similar between the PCI and exercise groups. Physical activity patterns will be monitored in a similar fashion in both the PCI and exercise groups.

5. Cost effectiveness analysis

The cost analysis will examine two research questions:

1. Does exercise training reduce healthcare costs as compared to standard PCI after 1-year? and
2. Is a program of exercise rehabilitation more cost-effective compared to PCI?

These findings are considered preliminary for a larger study, given the study's sample size. In order to derive all the necessary information related to the cost analyses, only subjects who receive their routine care at the VA Palo Alto HCS are recruited for the study (approximately 97% of patients referred for PCI receive their care at our facility).

For the purpose of this cost analysis, *"effectiveness"* of the intervention is defined by the primary outcome at the patient level. That is, changes from baseline in individual global myocardial perfusion pattern with dipyridamole at 1-year is used to calculate the effect. Individual level change scores are associated with individual intervention net-costs (intervention delivery minus healthcare expense cost-savings), to provide confidence intervals of each economic value.

5.1. Estimating intervention's costs and healthcare expenses

The cost identification analysis is from the provider's (VA's) perspective because of the life-long entitlement of VA services for veterans. We identify the VA expense to produce the service in each intervention or study arm. In addition, since we hypothesize a net cost-savings to the VA in the long-run, we must collect the VA healthcare utilization during the study period and estimate the total expense. This valuation step is complicated by the current state of cost accounting in the VA. Both the internal VA Decision Support System (DSS) valuation and an external reference created from national Medicare reimbursement values are being used [53,54]. We have previously used the VA DSS to evaluate health care costs associated with fitness [55–57] and physical activity patterns [58]. This approach is consistent with the VA HSR&D Services' Health Economics Resource Center's (HERC) 2002 recommendations, as long as everything is within one facility.

5.2. Intervention's delivery expense

We initially estimate the cost of delivering care for the intervention and for routine care (PCI). The incremental cost of production for the intervention is expected to be the additional personnel time required to add the incremental intensity of care. We are following the framework proposed by Donaldson [59] where personnel, materials, supplies and space are included in this estimate. To the extent possible, DSS data is being used, which is a micro-costing approach. Such cost-identification must be at the patient-level with comparison of means at the group level in order to gain confidence intervals of the estimates.

5.3. Intervention cost identification data collection

The provider's perspective constrains cost identification to the local facility's personnel time, materials, procedures, etc. The VA computerized medical records system (CPRS) template of patient encounter times, personnel and procedures, and medications involved is quantified. This will document the appropriate expenses. Base salary and fringe for all personnel involved with the patient is being determined from personnel files. Space required for each encounter will be identified and valued by VA estimates.

5.4. Healthcare utilization and expense estimates

The delivery costs must then be offset by the healthcare cost-savings (as compared to the non-intervened group) based in VA healthcare utilization for each patient to acquire the net cost-savings. The difference between the means of each group, after ranking in effectiveness order, provides the incremental cost of the cost-effectiveness analysis. Issues of discounting dollar amounts for inflation and time value of money are handled by sensitivity analysis and methods consistent with Gold et al. [60]. Concerns for patient preferences and a societal estimation are not addressed in this study.

5.5. VA utilization extractions and cost-savings estimates

Using the VA system (CPRS), we are tracking the actual patient care utilization (e.g., inpatient and outpatient visits, events, hospitalizations, procedures and prescriptions) during the study period for each patient in the trial. This permits the comparison of the expected differences in hospitalizations, physician visits, medications and ER visits. The difference in units of service (physician / primary care visits; ER visits and hospitalizations) are being valued using the Medicare national average, without differentials for teaching affiliation and geographic location, and by national average DSS values from the VA. Medical events are chronologically ordered for each patient, and reassembled into one-year episodes of care for both pre- and post intervention periods to acquire the cost-savings impact of the intervention at the patient-level. Thus, a patient's individual cost-savings as well as a comparison against the routine care group's mean will be obtained.

6. Discussion

Exercise and lifestyle interventions are underutilized strategies in the management of patients with CVD pre- and post-revascularization despite their potential value. Although coronary interventions are part of routine practice, they are often driven by economic factors while minimal attention is given to which patients may benefit the most from them. This partly explains the low overall referral rate to cardiac rehabilitation in the US (reported to be only 10–20% of eligible patients [61,62]). This pattern persists even though rehabilitation programs result in physiologic adaptations not achievable with PCI alone, including improved functional capacity, enhanced endothelial function, skeletal muscle metabolic changes, and improved risk factor profiles [15,27,28,33,63]. The PAUSE trial extends previous studies that have

documented the benefits of cardiac rehabilitation by using newer, non-invasive technologies to quantify coronary anatomy and perfusion following exercise training and lifestyle intervention. In addition, the trial quantifies clinical outcomes, risk markers, and quality of life in patients randomized to PCI or exercise training. Moreover, this is the first randomized trial to our knowledge to systematically assess cost-effectiveness of rehabilitation compared to PCI.

There have been major increases in the use of PCI in recent years, with considerable costs associated with it. While it is commonly assumed that PCI also reduces mortality, randomized trials have shown that PCI has minimal effect on 1- to 5-year mortality except patients with severe CAD or those treated for acute myocardial infarction [4,5,11,64]. For example, in the recent Objective Randomized Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA) trial, 230 patients with stable angina underwent randomization to receive PCI or a sham procedure [4]. There was no significant difference in the primary endpoint of exercise capacity between groups, no differences in angina symptoms and, importantly, there were no differences in myocardial infarction or mortality rates in patients who underwent PCI vs. controls. The observation that symptoms did not differ between groups is notable given that PCI is often performed to reduce angina symptoms. In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, a VA Cooperative study comparing PCI to optimal medical therapy in 2287 patients with chronic stable angina, PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events compared to optimal medical therapy [5]. In a substudy of the COURAGE trial, the added cost of PCI versus optimal medical therapy was approximately $10,000 USD per patient, with no benefits in terms of life-years or quality-adjusted life years gained [65]. In another substudy of COURAGE focusing on the effect of PCI on quality of life, it was demonstrated that the cost for 1 patient to have a clinically significant improvement in angina exceeded $100,000 [66]. The ORBITA, COURAGE, and other trial results demonstrate that it is safe to defer PCI in selected patients with symptomatic CAD, and deferring PCI achieves an appreciable savings in health care expenditures. In light of recent trials demonstrating benefits in coronary vascular function, coronary risk, and cost savings attributable to exercise training in patients with stable symptomatic CAD [28,40,63], it is possible that the addition of an exercise program to optimal medical therapy in PCI candidates would result in even better outcomes and cost savings.

There is a need to evaluate more judicious use of PCI and to consider less costly interventions for at least some of the > 1.3 million patients in the U.S. who undergo this procedure each year. Lifestyle intervention, including exercise training, is one option that has been shown to result in reduced symptoms, better exercise tolerance, improved quality of life and lower mortality [40,28,63]. A growing body of data has demonstrated that exercise intervention improves coronary anatomy and lessens ischemia through enhanced endothelial function [33,40,63,67]. While a significant proportion of health care expenditures are devoted to PCI and other invasive interventions for CVD, few health care resources are directed toward primary or secondary prevention. Recent studies have demonstrated that programs of cardiac rehabilitation, with and without implementation of intensive risk reduction, are cost effective [40,63,68]. We [56–59] and others [68] have observed that higher physical activity patterns, higher levels of fitness, or both, are associated with lower health care costs. Prospective trials such as the INTERHEART [70] and HALE [71] studies, and long-term observational studies including the Nurses' Health Study [72], the Health Professionals Follow-up Study [73], and the Veterans Exercise Testing Study (VETS) [16,17,34,74], have shown that lifestyle factors, including physical activity, fitness, smoking cessation, and dietary intervention have a major impact on cardiovascular and all-cause mortality. Preventive health strategies with the potential to decrease health care costs are of critical importance in the US and elsewhere, and these latter studies provide an economic-based impetus for health care providers and health systems to promote physical activity.

6.1. Summary

We anticipate that the current study will add to a growing body of data suggesting that many patients benefit from optimal medical management to an extent that is similar to PCI. Previous comparisons between PCI and optimal medical management have lacked an exercise intervention component, and the PAUSE trial extends these studies by adding case-managed exercise training to optimal medical management. This approach could also provide an impetus to refer patients to rehabilitation programs as a complement to PCI [75], or as an alternative to PCI in selected patients [40]. It may also add support to the concept that patients evaluated for ischemia can exercise safely and effectively in a supervised setting with support of the primary care provider or cardiologist. In addition, there is a large “wait and see” population, in whom PCI is not critically urgent, who can not only benefit from exercise therapy, but can also improve both their long-term prognosis and reduce health care costs. At minimum, the available data to date provides additional groundwork for expanding the population that can potentially benefit from exercise therapy, particularly given the poor referral rates to cardiac rehabilitation programs [62].

Funding

This study was funded by the Veterans Administration Rehabilitation Research and Development Service, Grant #B0344-1

References

[1] E.J. Benjamin, S.S. Verani, C.W. Callaway, et al., American Heart Association, Heart disease and stroke statistics, 2018 update, Circulation 137 (2018) e67–e492.
[2] American Heart Association CVD burden report, Cardiovascular Disease: A Costly Burden for America- Projections through 2035, http://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_491543.pdf , Accessed date: 13 April 2018.
[3] J. Ryan, D.J. Cohen, Are drug-eluting stents cost-effective? It depends on whom you ask, Circulation 114 (2006) 1736–1744.
[4] R. Al-Lamee, D. Thompson, D. Hakim-Moulay, S. Sen, K. Tang, J. Davies, et al., Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomized controlled trial, Lancet 391 (2018) 31–40.
[5] W.E. Boden, et al., Optimal medical therapy with or without PCI for stable CAD (COURAGE), N. Engl. J. Med. 356 (2007) 1503–1516.
[6] E.D. Peterson, J.S. Rumsfeld, Finding the courage to reconsider medical therapy for stable angina, N. Engl. J. Med. 359 (2008) 751–753.
[7] M. Dellborg, PCI in ST-elevation infarction—one flew over the cuckoo's nest, Scand. Cardiovasc. J. 4 (2006) 8–10.
[8] C.L. Tommaso, One year perspective on COURAGE, Catheter. Cardiovasc. Interv. 72 (2008) 426–429.
[9] P. Joseph, K. Teo, Optimal medical therapy, lifestyle intervention, and secondary prevention strategies for cardiovascular event reduction in ischemic heart disease, Curr. Cardiol. Rep. 13 (2011) 287–295.
[10] J.P. Curtis, Y. Wang, et al., All-cause readmission and repeat revascularization after percutaneous coronary intervention in a cohort of Medicare patients, J. Am. Coll. Cardiol. 54 (2009) 903–907.
[11] D.R. Homes, B.J. Gersh, et al., Percutaneous coronary intervention for chronic stable angina, J. Am. Coll. Cardiol. 1 (2008) 34–43.
[12] J. Myers, P. McAuley, C.J. Lavie, J.P. Despres, R. Arena, P. Kokkinos, Prog. Cardiovasc. Dis. 57 (2015) 306–314.
[13] D. Hansen, M.F. Piepoli, W. Doehner, The importance of rehabilitation in the secondary prevention of cardiovascular disease, Eur. J. Prev. Cardiol. (2018), https://doi.org/10.1177/2047487318809459.
[14] J. Myers, The new AHA/ACC guidelines on cardiovascular risk: when will fitness get the recognition it deserves? Mayo Clin. Proc. 89 (2014) 722–726.
[15] P.D. Thompson, D. Buchner, I.L. Pina, et al., Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the council on clinical physical activity, and metabolism (subcommittee on physical activity), Circulation 107 (2003) e42–e49.
[16] P. Kokkinos, J. Myers, C. Faselis, D. Panagiotakos, et al., Exercise capacity and mortality in older men: a 20 year follow-up study, Circulation 122 (2010) 790–797.
[17] J. Myers, M. Prakash, V. Frolicker, D. Do, et al., Exercise capacity and mortality among men referred for exercise testing, N. Engl. J. Med. 346 (11) (2002) 793–801.
[18] M. Haber, L. Kaminsky, R. Arena, S. Blair, et al., Impact of cardiorespiratory fitness on all-cause and disease-specific mortality: advances since 2009, Prog. Cardiovasc. Dis. 60 (1) (2017) 11–20.
[19] R. Ross, S. Blair, R. Arena, T. Church, J.P. Despres, B. Franklin, W. Haskell,

B. Levine, C.J. Lavie, J. Myers, J. Niebauer, R. Sallis, S. Sawada, X. Sui, U. Wisloff, Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign. An American Heart Association scientific statement from the committee on physical activity and the council on lifestyle and cardiometabolic health, Circulation 134 (2016) e653–e699.
[20] K. Morrow, C.K. Morris, V.F. Froelicher, et al., Prediction of cardiovascular death in men undergoing noninvasive evaluation for coronary artery disease, Ann. Intern. Med. 118 (1993) 689–695.
[21] V. Raxwal, K. Shetler, A. Morise, D. Do, J. Myers, J.E. Atwood, V.F. Froelicher, Simple treadmill score to diagnose coronary disease, Chest 119 (2001) 1933–1940.
[22] J. Myers, D. Do, W. Herbert, P. Ribisl, V. Froelicher, A nomogram to predict exercise capacity from a specific activity questionnaire and clinical data, Am. J. Cardiol. 73 (1994) 591–596.
[23] J. Myers, N. Buchanan, et al., Comparison of the ramp versus standard exercise protocols, J. Am. Coll. Cardiol. 17 (1991) 1334–1342.
[24] G.A.V. Borg, Borg's Perceived Exertion and Pain Scales, Human Kinetics, Champaign, IL, 1998.
[25] P. Shue, V. Froelicher, EXTRA: an expert system for exercise test reporting, J. Non-Invas. Test II-4 (1998) 21–27.
[26] D.B. Mark, M.A. Hlatky, et al., Exercise treadmill score for predicting prognosis in coronary artery disease, Ann. Intern. Med. 106 (1987) 793–800.
[27] G.F. Fletcher, P.A. Ades, P. Kligfield, et al., Exercise standards for testing and training: a scientific statement from the American Heart Association, Circulation. 128 (8) (2013) 873–934.
[28] American Association of Cardiovascular and Pulmonary Rehabilitation, Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs, 5th edition, Human Kinetics, Champaign, 2017.
[29] American College of Sports Medicine, Guidelines for Exercise Testing and Prescription, 10th edition, Lippincott, Williams & Wilkins, Baltimore, 2018.
[30] K. Stewart, B. Franklin, R. Squires, Resistance training in patients with coronary heart disease. In Graves JE and Franklin BA, Resistance Training in Health and Rehabilitation, Human Kinetics, Champaign, 2001, pp. 217–236.
[31] B. Humphries, E. Dugan, TLA D: muscular fitness, American College of Sports Medicine Resource Manual for Guidelines for Exercise Testing and Prescription, LW &W, Baltimore, 2006.
[32] B.E. Ainsworth, W.L. Haskell, et al., Compendium of physical activities: an update of activity codes and MET intensities, Med. Sci. Sports Exerc. 32 (2000) S498–S504.
[33] J. Myers, Exercise and fitness, in: J. Perk (Ed.), Cardiovascular Prevention and Rehabilitation, Springer, London, 2007, pp. 77–87.
[34] J. Myers, A. Kaykha, S. George, et al., Fitness versus physical activity patterns in predicting mortality in men, Am. J. Med. 117 (2004) 912–918.
[35] R.S. Paffenbarger, R.T. Hyde, A.L. Wing, et al., Some interrelations of physical activity, physiological fitness, health, and longevity, in: C. Bouchard, R.J. Shephard, T. Stephens (Eds.), Physical Activity, Fitness, and Health, Champaign, IL, Human Kinetics, 1994, pp. 119–133.
[36] S. Dorbala, M.F. Di Carli, Cardiac PET perfusion: prognosis, risk stratification, clinical management. Semin. Nucl. Med. 44 (2014) 344–357.
[37] R. Belardinelli, I. Paolini, G. Cianci, R. Piva, D. Georgiou, A. Purcaro, Exercise training intervention after coronary angioplasty: the ETICA trial, J. Am. Coll. Cardiol. 37 (2001) 1891–1900.
[38] K. Yoshinaga, R.S.B. Beanlands, R.A. deKemp, M. Lortie, J. Morin, M. Aung, R. Mcelvie, R.F. Davies, Effect of exercise training on myocardial blood flow in patients with stable coronary artery disease, Am. Heart J. 151 (132) (2006) 4e11–1324e18.
[39] R.A. Goldstein, R.L. Kirkeeide, R.W. Smalling, A. Nishikawa, M.E. Merhige, L.L. Demer, N.A. Mullani, L. Gould, Changes in myocardial perfusion after PTCA: non-invasive assessment with PET, J. Nucl. Med. 28 (1987) 1262–1267.
[40] R. Hambrecht, C. Walther, et al., Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease; a randomized trial, Circulation 109 (2004) 1371–1378.
[41] G. El Fakhri, A. Kardan, A. Sitek, et al., Reproducibility and accuracy of quantitative myocardial blood flow assessment with 82 Rb PET: comparison with (13) N-ammonia PET, J. Nucl. Med. 50 (2009) 1062–1071.
[42] M.F. Di Carli, V.L. Murthy, Cardiac PET/CT for the evaluation of known or suspected coronary artery disease, Radiographics 31 (5) (2011) 1239–1254.
[43] M.J. Budoff, et al., Assessment of coronary artery disease by cardiac CT. AHA scientific statement, Circulation 114 (2006) 1761–1791.
[44] D. Kapoor, R. Thompson, Diagnostic accuracy of CT coronary angiography, Cardiol. Clin. 27 (2009) 563–571.
[45] F.Y. Lin, S.E. Zentco, J.K. Min, The prognostic value of cardiac computed angiography, Cardiol. Clin. 27 (2009) 573–585.
[46] E.U. Nitzsche, Y. Choi, J. Czernin, C.K. Hoh, S.C. Huang, H.R. Schelbert, Noninvasive quantification of myocardial blood flow in humans: a direct comparison of the [13N]ammonia and the [15O]water techniques, Circulation. 93 (1996) 2000–2006.
[47] S. Nagamachi, J. Czernin, A.S. Kim, et al., Reproducibility of measurements of regional resting and hyperemic myocardial blood flow assessed with PET, J. Nucl. Med. 37 (1996) 1626–1631.
[48] R. Campisi, J. Czernin, H. Schoder, J. Sayre, F. Marengo, M. Phelps, H.R. Schelbert, Effects of long-term smoking on myocardial blood flow, coronary vasomotion, and vasodilator capacity, Circulation. 98 (1998) 119–125.
[49] J. Czernin, P. Muller, S. Chan, R.C. Brunken, G. Porenta, J. Krivokapich, K. Chen, A. Chan, M.E. Phelps, H.R. Schelbert, Influence of age and hemodynamics on myocardial blood flow and flow reserve, Circulation. 88 (1993) 62–69.
[50] M. Cerqueira, N. Weissman, V. Dilsizian, A. Jacobs, S. Kaul, W. Laskey, D.J. Pennell, J. Rumberger, T. Ryan, M. Verani, Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart, Circulation. 105 (2002) 539–542.
[51] F.J.T. Wackers, Display and analysis of SPECT perfusion imaging, Nuclear Cardiology, The Basics, Second edition: How to Set Up and Maintain a Laboratory, Springer, 2008, pp. 129–171.
[52] S. Achenbach, F. Moselewski, D. Ropers, M. Ferencik, U. Hoffmann, B. MacNeill, K. Pohle, U. Baum, K. Anders, I. Jang, W. Daniel, T. Brady, Detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, sub-millimeter multidetector spiral computed tomography: a segment-based comparison with intravascular ultrasound, Circulation. 109 (2004) 14–17.
[53] M.K. Chapko, J.L. Ehreth, S. Hedrick, Methods of determining the cost of health care in veterans affairs medical centers and other non-priced settings, Eval. Health Prof. 14 (1991) 282–303.
[54] P.G. Barnett, J.H. Rodgers, Use of the decision support system for VA cost-effectiveness research, Med. Care 37 (1999) AS63–70.
[55] J.P. Weiss, V.F. Froelicher, J. Myers, Health care costs and exercise capacity, Chest 126 (2004) 608–613.
[56] J. Myers, R. Doom, R. King, H. Fonda, J. Abella, V. Froelicher, K. Chan, P. Kokkinos, Association between cardiorespiratory fitness and health care costs: the veterans exercise testing study, Mayo Clin. Proc. 93 (2018) 48–55.
[57] Grüne de Souza de Silva C, Kokkinos P, Doom R, Loganathan D, Fonda H, Chan K, Soares de Araújo CG, Myers J. Association between cardiorespiratory fitness, obesity, and health care costs: the Veterans Exercise Testing Study. Int. J. Obes., 2018, (in press).
[58] A. Ghayoumi, J. Myers, et al., Physical activity patterns and health care costs, JACC 45 (2005) 16A.
[59] C. Donaldson, The state of the art of costing health care for economic evaluation, Commun. Health Stud. 24 (1990) 341–356.
[60] M.R. Gold, J.E. Siegel, L.B. Russell, M.C. Weinstein, Cost-Effectiveness in Health and Medicine, Oxford University Press, New York, 1996.
[61] J.A. Suaya, D.S. Shepard, S.L.T. Normand, P.A. Ades, J. Prottas, W.B. Stason, Use of cardiac rehabilitation by Medicare beneficiaries after myocardial infarction or coronary bypass surgery, Circulation 116 (2007) 1653–1662.
[62] R. Arena, M. Williams, D. Foreman, L. Cahalin, L. Coke, J. Myers, L. Hamm, P. Kris-Etherton, R. Humphrey, V. Bittner, C. Lavie, Increasing referral and participation rates to outpatient cardiac rehabilitation: the valuable role of healthcare professionals in the acute care and home health settings. A scientific statement from the American Heart Association Council on exercise, prevention, and rehabilitation, Circulation 125 (2012) 1–9.
[63] P.A. Ades, Cardiac rehabilitation and secondary prevention of CHD, N. Engl. J. Med. 346 (2002) 379–380.
[64] S.R. Mehta, C.P. Cannon, K.A. Fox, et al., Routine vs. selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials, JAMA 293 (2005) 2908–2917.
[65] W.S. Weintraub, W.E. Boden, et al., Cost-effectiveness of percutaneous coronary intervention in optimally treated stable coronary patients, Circulation 1 (2008) 12–20.
[66] W.S. Weintraub, J.A. Spertus, et al., Effect of PCI on quality of life in patients with stable coronary disease, N. Engl. J. Med. 359 (2008) 677–687.
[67] R. Hambrecht, A. Wolf, S. Gielen, et al., Effect of exercise on coronary endothelial function in patients with coronary artery disease, N. Engl. J. Med. 342 (2000) 454–460.
[68] A.J. Lee, G.K. Strickler, et al., The economics of cardiac rehabilitation and lifestyle modification: a review of literature, J. Cardpulm. Rehabil. Prev. 27 (2007) 135–142.
[70] S. Yusuf, S. Hawken, S. Ounpuu, et al., Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study), Lancet 364 (2004) 937–952.
[71] K.T. Knoops, et al., Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project, JAMA 292 (2004) 1433–1439.
[72] 72. M.J. Stampfer, F.B. Hu, J.E. Manson, et al., Primary prevention of coronary heart disease in women through diet and lifestyle, N. Engl. J. Med. 343 (2000) 16–22.
[73] H.C. Hung, K.J. Joshipura, et al., Fruit and vegetable intake and risk of major chronic disease, J. Natl. Cancer Inst. 96 (2004) 1577–1584.
[74] P. McAuley, J. Pittsley, J. Myers, et al., Fitness and fatness as mortality predictors in healthy older men: the Veterans Exercise Testing Study, J. Gerontol. A Biol. Sci. Med. 64 (2009) 695–699.
[75] M. Bäck, B. Wennerblom, et al., Effects of high frequency exercise in patients before and after elective percutaneous coronary intervention, Eur. J. Cardiovasc. Nurs. 78 (2008) 307–313.