Cover Page

Study Title: PCI Alternative Using Sustained Exercise (PAUSE)
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Statement of the Problem

Cardiovascular disease (CVD) remains the most common cause of death in the United States. CVD currently claims nearly one million lives yearly in the U.S., accounting for nearly 40% of all deaths (1). The total cost of cardiovascular disease in the U.S., including hospitalizations and lost productivity, is approximately $300 billion annually (1,2). Coronary artery disease (CAD) accounts for the largest number of deaths and the majority of these costs. While the efforts aimed at treating this disease in recent decades have concentrated on surgical and catheter-based interventions, limited resources have been directed toward primary prevention and rehabilitation (3,4).

Over the last decade, the use of percutaneous coronary intervention (PCI) has increased exponentially. Between 1996 and 2007, the number of PCIs performed in the U.S. increased more than 4-fold, from approximately 300,000 to more than 1.3 million yearly (1). During this time, PCI has accounted for 10% of the overall increase in Medicare expenditures (5). In light of the extraordinary increase in the use of this technology in recent years, 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 (5-9). Despite the fact that PCI is expensive, repeat PCI is not unusual (10) and there is no evidence for improved survival (11), alternative therapies are rarely considered. One alternative therapy that has been shown to improve outcomes in PCI candidates is intensive lifestyle intervention, including exercise training. In the PCI vs. Exercise Training (Leipzig) study (12), PCI candidates randomized to one year of exercise training had improved coronary anatomy, higher exercise capacity, an improvement in quality of life and event-free survival, as well as lower health care costs when compared to the PCI group. However, the Leipzig study employed invasive angiographic methods which do not provide information on dynamic coronary flow or atherosclerosis specifically, and do not provide insight into the mechanism of atherosclerosis progression or regression (13). In addition, economic analyses were limited to cost per change in Canadian Cardiovascular Society Class; the Leipzig study did not assess *cost-effectiveness*.

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 in PCI candidates, the current proposal is 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 greater improvement in coronary function and anatomy compared to those randomized to PCI.** Both groups will receive optimal medical management. We will also compare health care costs, symptoms, quality of life, and clinical outcomes between the two groups. At baseline and one year after randomization, patients will undergo an assessment of physical activity patterns and fitness using standardized questionnaires and maximal cardiopulmonary exercise testing (CPX). Patients will also undergo evaluation of coronary function and anatomy with positron emission tomography combined with computed tomographic angiography (PET/CTA). PET will be used to measure myocardial perfusion. CTA will be used to evaluate anatomical progression of atherosclerotic disease based on a qualitative scoring system of coronary artery calcium. The combination of PET/CTA provides information that previously could only be obtained invasively using coronary flow wires and invasive x-ray angiography. This will permit a non-invasive way to evaluate both functional and anatomical adaptations to exercise. Our overall objective is to demonstrate the utility of a non-invasive technology to document the efficacy of exercise therapy as an alternative treatment strategy to PCI for coronary lesions.

Key Questions and Hypotheses

Key Questions

1) Does exercise training favorably alter coronary anatomy and function as determined by non-invasive imaging techniques?
2) Can a program of exercise therapy improve outcomes (exercise capacity, symptoms, repeat hospitalizations, and quality of life) in patients with CAD that are equivalent or superior to PCI?
3) Will exercise training and intensive risk reduction reduce costs as compared to standard PCI after 1-year?

Specific Objectives

Principal Objective. The principal objective of this proposal is to determine if a program of exercise training improves coronary function and anatomy measured by non-invasive imaging.

Secondary Objective #1. To compare the effects of exercise training to PCI on clinical and functional outcomes in patients with CAD.

Secondary Objective #2. To determine whether a 1-year program of exercise intervention will save health care costs compared to PCI.

BACKGROUND

Rationale for the Current Proposal

Despite advances in treatment options for CVD, this condition remains the leading cause of morbidity and mortality in the U.S. and is a major cause of disability in Veterans (1). PCI is the treatment most often used in patients with various manifestations of CAD. It is often used as an intervention for those experiencing *acute coronary syndrome* (ACS), an umbrella term that describes a group of clinical symptoms associated with acute myocardial ischemia. PCI usually involves coronary angioplasty with permanent placement of a stent. This procedure has been shown to reduce symptoms due to CAD and to reduce ischemia (11). In recent years, drug eluding stents (DES) have been shown to reduce the high re-stenosis rate associated with bare metal stents (BMS). However, the cost of DES is 3 to 5 times higher than BMS and requires long term antiplatelet therapy (14). While it is commonly assumed that PCI also reduces mortality, randomized trials have shown that PCI has no effect on 1- to 5-year mortality except in patients being treated for acute myocardial infarction (6,11,15).

There have been major increases in the use of PCI over the last decade, with major costs associated with it. In a recent sub-study of the COURAGE trial, a VA Cooperative study comparing PCI to optimal medical therapy in 2,287 patients with chronic stable angina, the added cost of PCI versus optimal medical therapy was approximately $10,000, with no benefit in terms of life-years or quality-adjusted life years gained (16). In another sub-study 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 (17). The COURAGE results demonstrate that it is safe to defer PCI in patients with symptomatic chronic coronary disease, 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 (12,18,19,20), 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.

Cost analyses have suggested that the current rate of increase in PCI with DES is unsustainable for the U.S. healthcare system (5). Given the high costs associated with PCI, there have been recent efforts to compare outcomes and effectiveness of PCI against non-invasive therapy. In the Occluded Artery Trial (OAT) (21), cumulative 2-year costs were $7,000 lower in patients randomized to medical therapy versus PCI, and medical therapy was associated with slightly better quality-adjusted survival. In the primary COURAGE trial (6), PCI did not reduce the risk of mortality, myocardial infarction, or other cardiovascular events when compared to optimal medical therapy over 4.6 years of follow-up. Interestingly, in an additional sub-analysis of COURAGE assessing myocardial perfusion data (22), a greater improvement in percent of ischemic myocardium, a predictor of mortality, was observed in patients who underwent PCI. Although the myocardial perfusion results were conflicting to the main trial results, not all patents had myocardial perfusion evaluations performed and the sample in the sub-study was not randomized. In addition, the study did not include an evaluation of endothelial dysfunction, which has been associated with cardiac events and has been reported in post-PCI patients with DES. The COURAGE trial has stimulated a great deal of media attention and numerous commentaries. Interpretations of the COURAGE results range from confirmation of PCI as it is presently indicated by recognized guidelines, to recommending a greater emphasis on aggressive medical and lifestyle therapy in selected patients in lieu of PCI, to predicting a marked decline in PCIs (7,9,23).

There is a need to evaluate more judicious use of PCI, and to consider less costly interventions for at least some of the more than 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 (18). A growing body of data has demonstrated that exercise intervention improves coronary anatomy and lessens ischemia through enhanced endothelial function (12,18,19,24). 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 (18,20). We (25) and others (26) have observed that higher physical activity patterns, higher levels of fitness, or both, are associated with lower health care costs. Recent prospective trials such as the INTERHEART (27) and HALE (28) studies, and long-term observational studies including the Nurses' Health Study (29), the Health Professionals Follow-up Study (30), and the Veterans Exercise Testing Study (VETS) (31,32), have shown that lifestyle factors, including physical activity, fitness, smoking cessation, and dietary intervention have a major impact on cardiovascular and all-cause mortality. In the INTERHEART study, a case-control evaluation of risk factors for acute myocardial infarction in 52 countries, it was demonstrated that 9 preventable risk factors explained 90 and 94% of the incidence of myocardial infarction in men and women, respectively (27). Importantly, simply removing smoking as a risk factor, adding a modest amount of weekly exercise (approximately 30 minutes/day), and including fruits and vegetables in the diet led to an approximate 80% lower risk of cardiac events. These results were similar to those from the Nurses' Health Study, which demonstrated that 75% of the risk for MI or stroke would be removed by these 3 risk factors in women (29).

Only one randomized, controlled study has compared exercise and lifestyle intervention with PCI. Hambrecht and colleagues (12) studied 100 candidates for PCI who were randomized to either one year of at-home rehabilitation or to PCI and standard medical therapy (the PCI vs. Exercise Training [Leipzig] Study). The subjects underwent baseline and repeat cardiac catheterization, maximal exercise testing, assessment of quality of life, and an analysis of the cost-effectiveness of each treatment. After one year, patients randomized to the exercise training group had improved coronary anatomy, higher exercise capacity, an improvement in quality of life, better event-free survival, and lower health care costs when compared to the PCI group. In a 2-year follow-up to this study, the event-free survival rate remained significantly lower in the exercise group compared to the PCI group, and inflammatory markers were significantly reduced in those

randomized to exercise. Many studies have demonstrated favorable effects of exercise training on endothelial function in the upper and lower limbs, including endothelial-dependent vasodilation, arterial flow reserve and other measures of vascular health (18,19,24). Hambrecht et al (19) were the first to demonstrate that supervised exercise training in patients with CAD improves endothelial-dependent vasodilation in the *coronary vessels*.

Gaps in the Current Literature to be Filled by the Proposed Study

While the PCI vs. Exercise Training Study generated a great deal of interest in both the lay press and the Cardiology community, there have been no efforts to replicate its results. In part because of the financial interests associated with PCI, exercise and lifestyle intervention is rarely considered as a clinical treatment option in PCI candidates. Although the COURAGE trial (6) underscored the lack of effect of PCI on outcomes, and showed that medical therapy in lieu of PCI substantially reduced costs, "optimal" medical therapy would include exercise and lifestyle intervention, and this was not studied. A gap exists between the standard clinical treatment for CAD and the potential for non-invasive, less expensive and potentially more effective treatments for these patients. Previous efforts to quantify the effects of exercise-based rehabilitation on coronary artery perfusion and anatomy have been limited to standard angiography, and have largely been performed prior to the statin era (generally considered to be prior to the mid-1990s).

New Measurement Techniques that Facilitate Improved Outcome Measurement

In recent years, improved technologies for imaging coronary perfusion and anatomy have been developed which could provide important insights into the effects of exercise training on the heart. These include the combination of positron emission tomography (PET) and ultra-fast computed tomography angiography (CTA), commonly termed PET/CTA. PET provides information on the functional significance of stenosis by accurately quantifying global perfusion, whereas CTA evaluates the anatomical severity of stenosis and the degree of calcified and noncalcified plaque burden (33). The combination of computed tomography with PET also allows for improved attenuation correction. The combination of both functional and anatomical information to be used in this study provides a more comprehensive evaluation than available in previous studies. The combination of these two technologies also provides information that previously could only be obtained invasively using coronary angiography and coronary flow wires. The potential for these newer methods to study coronary anatomy and perfusion after exercise-based rehabilitation has not been previously explored.

Purpose of the Current Proposal

We have termed the current proposal "**P**CI **A**lternative **U**sing **S**ustained **E**xercise" (PAUSE) to reflect the potential for exercise training as an alternative therapy that should be considered before an invasive option for select PCI candidates. The primary aim of this proposal is to determine whether subjects with lesions amenable to PCI randomized to a 1 year exercise program have greater improvement in coronary perfusion and function than those randomized to PCI alone. As secondary analyses, we will compare exercise capacity, health care costs, quality of life, and clinical outcomes between groups. Our institution is well-equipped to conduct such a study given that the research focus of the investigators has long been directed toward the areas of exercise training in cardiovascular disease and cardiac imaging, and all of the staff and resources necessary to perform the study are in place.

Significance of the Current Proposal

Exercise and lifestyle interventions are underutilized strategies in the management of patients with CVD post-revascularization despite their potential value. Although coronary interventions are part of routine practice, they are often driven by economic factors while little 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 12% of eligible patients in a recent

meta-analysis (34)). 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 (18,19,24). The current proposal 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, this proposal will quantify clinical outcomes, risk markers, and quality of life in patients randomized to PCI or exercise training. Moreover, this study will be the first randomized trial to systematically assess cost-effectiveness of rehabilitation compared to PCI.

PCI is often the preferred choice for patients and providers for immediate symptomatic relief despite lack of evidence supporting a mortality benefit with PCI. The potential value of rehabilitation is underscored by the observation that outcomes are improved among patients who participate in such programs (18,19,24,35-37). A recent Cochrane meta-analysis demonstrated a 27% reduction in total mortality and a 31% reduction in cardiac mortality among patients randomized to exercise training compared to usual care (35). This is in agreement with earlier meta-analyses of randomized trials performed in the 1970s and 1980s, demonstrating reductions in cardiovascular morbidity and mortality from 20 to 30% among subjects randomized to rehabilitation (36,37). The benefits of exercise and lifestyle changes have also been documented by direct comparison to an interventional strategy; in the widely-cited Leipzig study, 12 months of exercise training in stable CAD patients was associated with better event-free survival, better coronary anatomy, and lower costs as compared to PCI (12). Although PCI has well-documented benefits for symptom relief, mortality benefits with PCI have not been demonstrated. A recent meta-analysis of 61 controlled trials reported that PCI had no benefit on mortality or myocardial infarction compared to medical therapy in non-acute coronary artery disease (38). Although exercise and lifestyle intervention have well-documented benefits on cardiovascular morbidity and mortality (4,12,18,24,26,35), this approach is rarely applied in candidates for PCI. The current proposal could provide an impetus to refer patients to rehabilitation programs as a complement to PCI (39), or as an alternative to PCI in selected patients (12). Our hypothesis is that a program of exercise-based rehabilitation will have greater improvement in overall coronary anatomy and myocardial perfusion and result in better outcomes, improved quality of life and will be more cost effective than PCI alone.

Relevance of the Proposed Work to the VA Patient Care Mission

CVD remains the leading cause of morbidity and mortality in the U.S. and is a major cause of disability in Veterans. The morbidity and mortality associated with CVD among Veterans virtually equals that of all other diseases combined, and the prevalence of cardiovascular disease in Veterans has been shown to be higher than that in non-Veterans (40). Despite well-documented benefits of exercise training and lifestyle intervention in patients with CVD, these interventions are greatly underutilized (4,18,34). Moreover, despite a 2002 VA directive encouraging the use of cardiac rehabilitation, such programs are scarce in the VA system. Rehabilitation as an intervention is often overlooked because clinicians tend to focus on repairing the coronary circulation and the potential need for revascularization (4). Numerous recent studies have demonstrated that secondary prevention programs reduce health care costs (12,20). With appropriate recognition, treatment, and lifestyle intervention, many complications associated with CVD, including cardiovascular morbidity and mortality, could be reduced (4,12,18,26). In addition, the use of non-invasive imaging techniques to cost effectively risk stratify patients with coronary artery disease has the potential to more appropriately direct resources and further save health care costs. These methods have the potential to reduce the burden of cardiovascular disease in Veterans and could also be utilized in other high risk groups.

A 2008 sub-study of the COURAGE trial (a VA Cooperative study) (16) provides a framework to underscore the potential cost effectiveness of optimal medical therapy and exercise as alternatives to PCI. The COURAGE investigators observed that compared to optimal medical therapy, PCI added approximately $10,000 to treatment costs without a significant gain in

life-years or quality adjusted life years. Other analyses from COURAGE showed that costs significantly favored medical treatment; for example, the cost per quality life-year gained was $217,000, more than 4 times the common benchmark for cost efficacy (41). The proposed study would be the first to systematically compare costs between rehabilitation and PCI. By more appropriate and selective referral of patients to invasive strategies and a greater emphasis on rehabilitation and lifestyle changes, the potential cost savings to the VA system could be substantial.

The proposed study also follows the new and widely-discussed "integrated" model approach to health care (42,43). This approach strives to expand utilization of services yet reduce costs by restructuring health care delivery through utilization of non-physician, allied health professionals (nurse, exercise physiologist, dietician, etc.) to deliver services under physician guidance. It incorporates an integrated approach, in which broader health care needs are individualized and delivered by multidisciplinary teams. The goal is to provide patients with better access to more services and receive more direct contact with health professionals, but at lower cost since less physician time is required. Exercise-based rehabiltation and comprehensive risk reduction programs have recently been instrumental in the development of this approach (18,42-44), and these interventions offer ideal models with which to demonstrate the effectiveness of this integrated approach. The application of exercise training in the proposed study has the potential be a model for improved health care delivery and cost reduction in the VA.

PRELIMINARY STUDIES

The Co-PIs have previously conducted a 3-year NIH-funded Specialized Center of Research (SCOR) project of exercise training in patients with cardiovascular disease (45,46), and are currently conducting an NIH Specialized Center of Clinically-Oriented Research (SCCOR) project on the effects of exercise therapy in patients with abdominal aortic aneurism disease (47). The proposed project will use existing exercise testing and training facilities at the VA Palo Alto Medical Center, and methods similar to the current NIH SCCOR project will be used in the current proposal.

Dr. Myers' research focus has been in the areas of exercise testing, training, and epidemiology in patients with coronary artery disease, chronic heart failure, and spinal cord injury. Since January 1992, he has directed the exercise research laboratory at the Palo Alto VAHCS. Dr Myers has a more than 25 year body of work related exercise testing and training in patients with CVD. He has served on writing groups for guidelines developed by the American Heart Association (AHA), American College of Sports Medicine (ACSM), American Thoracic Society (ATS), American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), and the European Society of Cardiology Working Group on Prevention and Rehabilitation. He is a recent recipient of the AACVPR Established Investigator Award, and is a Senior Research Career Scientist Award recipient from the VA. The fifth edition of his textbook co-authored with Dr. Froelicher, "Exercise and the Heart: Clinical Concepts" was published in April 2006.

Dr. Myers has also published extensively in the area of exercise training among patients with chronic heart failure (CHF). The focus of these studies has been on the application of MRI to quantify the effects of training on the myocardial remodeling process. He and his colleagues were the first to employ this technology to address a controversy that arose in the 1990s, in which it was suggested that exercise training could lead to myocardial damage. Using a high intensity training protocol and a series of randomized trials, it was demonstrated that training did not cause further myocardial damage among patients with CHF (48-50). These results have since been confirmed by studies performed in Italy, Canada, the US and elsewhere, and have been influential in the development of rehabilitation guidelines in these patients. Dr. Myers' followed these initial studies by applying a novel MRI tagging technique, in which the myocardium could be visualized more closely in 3 dimensions, including rotational displacement during systole and diastole (51,52). These studies demonstrated no adverse effects of training on myocardial size, function, or

rotation velocity during systole up to one year after undergoing training, and an improvement in relaxation velocity in a subgroup of patients with non-ischemic cardiomyopathy.

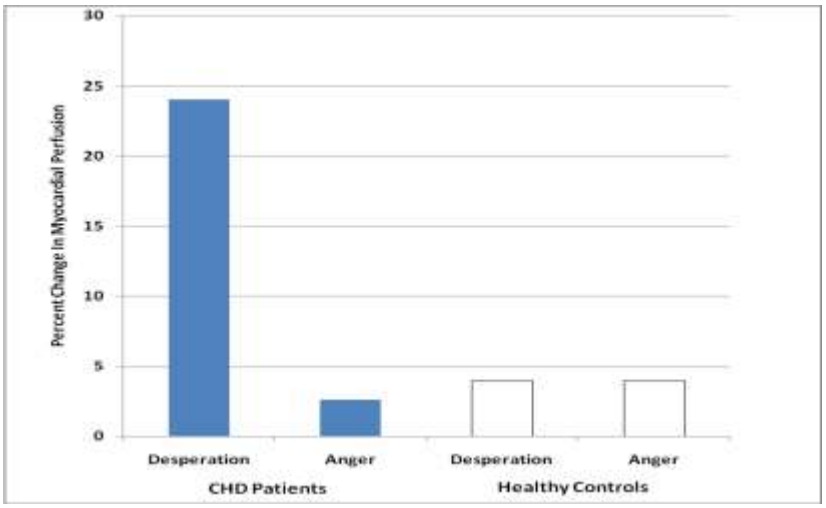
Dr. Froelicher has directed the ECG Department and Clinical Exercise Laboratory at the Palo Alto VA since 1992 and has considerable experience in the epidemiological study of cardiovascular disease as well as interpretation and application of exercise testing and training responses. Along with Dr. Myers, he has conducted numerous studies related to exercise testing, training, and cardiovascular health. Dr. Froelicher has a well-established reputation for his 35-year body of work in these areas. He has been instrumental in the development of prediction equations in patients undergoing evaluation for heart disease. These equations are reflected in the recent editions of the AHA/ACC Guidelines on Exercise Testing and elsewhere. While at the Long Beach and Palo Alto VA Health Care Systems, he has performed some of the largest outcome studies among Veterans. A salient feature of this research has been the observation that non-invasive variables (standard clinical and exercise test) can accurately stratify patients into high and low risk categories, and his prediction scores have been widely applied to help direct invasive procedures to patients who are most likely to benefit from them. Dr. Froelicher is a founding Fellow of the AACVPR, and the founding editor of the Journal of Cardiopulmonary Rehabilitation and Prevention.

The Co-PIs previously collaborated on an NIH SCOR project entitled, Perfusion, Performance, and Exercise Trial (PERFEXT) (45,46). This study involved the effects of 1-year of exercise training on myocardial perfusion and ventricular function in patients with coronary artery disease. Patients were randomized to a supervised exercise training program (n=72) or to usual care (n=74). Significant differences between groups were observed in thallium ischemia scores and ventricular function after 1 year, suggesting that training leads to a modest improvement in myocardial perfusion and that such changes can be detected non-invasively.

An ongoing NIH SCCOR project entitled, “Effects of exercise therapy in abdominal aortic aneurysm (AAA) disease” (Myers and Dalman, Co-PIs, Froelicher, Co-Investigator) is beginning its 4th year, and employs exercise testing and training methods that are similar to those in the current proposal. The purpose of the SCCOR project is to test the effectiveness of exercise training to reduce abdominal aortic aneurysm risk, limit small aneurysm progression, and modify biologic markers of AAA disease. The study includes 3 arms; one to identify signature protein profiles of AAA disease, another the application of MRI to develop and validate hemodynamic computational models in AAA progression, and the 3rd to investigate the effects of 3 years of exercise training on AAA size, aneurysm risk, and physiologic responses to exercise.

Dr. Nguyen is currently a staff physician at the Palo Alto VAHCS with an appointment in Cardiovascular Medicine at Stanford University. She has extensive experience using MRI, PET, and CTA to study coronary anatomy, cardiac function, and vasodilatory responses in patients with CVD. She has conducted studies on the application of novel MRI methods to diagnose significant coronary artery disease and impaired vasodilation to chemical and physical stimuli, an early marker of CVD. In a recent subset of 212 patients recruited from the **A**therosclerotic **D**isease, **VA**scular Functio**N** and Geneti**C** **E**pidemiology (ADVANCE) study, Dr. Nguyen observed that coronary artery vasodilation measured by MRI was highly correlated with physical activity patterns measured by total energy expenditure in kilocalories per kilogram per day (kcal/kg/day) (53). There was significant coronary artery vasodilation in response to nitroglycerin in both the less and more active patients, but the degree of coronary artery vasodilation was significantly higher in the active group. Regression analysis showed a strong correlation between the percentage vasodilation and the degree of physical activity, which remained significant after adjustment for major cardiac risk factors, coronary artery calcium scores, and use of vasoactive or statin medications. In addition, there was a positive relationship between coronary vasodilation and physical activity intensity. In another substudy from the ADVANCE trial, Dr. Nguyen evaluated the safety and efficacy of adenosine compared with regadenosine using PET in 2,015 patients with coronary disease (54). Similar test characteristics were observed between the two imaging agents, with better patient tolerance for regadenosine.

Dr. Segall, as Chief of the Nuclear Medicine Service at the VA Palo Alto Health Care System, will work closely with Dr. Nguyen and the Co-PIs to perform the PET/CT images. He has performed research in the area of nuclear imaging of the coronary vasculature, including PET, CT, and thallium SPECT for more than 20 years. He has experience using many different stress agents including dipyridamole, exercise, sestamibi, and emotional stress. The figure below shows changes in myocardial perfusion in one such study, in which patients with cardiovascular disease and healthy controls were studied using PET and psychological stress (55). The marked change in myocardial perfusion in response to one stressor is notable in the patients with cardiovascular disease. These observations are consistent with previous research showing that ischemic responses due to mental stress are found primarily in patients who demonstrate exercise-induced ischemia.



Dr. Bradham will perform the cost analyses for the study. He has previously collaborated with Dr. Myers on a VA RR&D Merit Review project entitled, "Customized Health Assessment and Risk Management" (CHARM), in which he performed cost-effectiveness analyses for an intensive cardiovascular risk reduction program in patients with spinal cord injury. Dr. Bradham is the VHA Health Economist at the Robert J. Dole VA Medical Center in Wichita, Kansas, and is a Health Economist in the VHA Cooperative Studies Program located in Perry Point, Maryland. From 2002 to 2008, he served the MS Center of Excellence (CoE) – EAST, in Baltimore, as Associate Director for Epidemiology and Outcomes, providing leadership to the CoE's mandated documentation of expenditures and VA healthcare use for MS in the VHA , and mentored junior investigators. Dr. Bradham has significant expertise in VHA databases, health economics, and health services research. He was an Expert Panel member of the HSR&D Service's Health Economics Resource Center (HERC) Advisory Board when the HERC was developing the VA's costing approaches for VHA. He has served on the Veterans Information Resource Center's (VIReC's) Data Request Review Board (DRRB) for the VA Medicare Data Merge Initiative. He was appointed to the Medicare Coverage Advisory Committee for the Centers for Medicare and Medicaid (CMS) in 2005 through 2007. His extensive experiences in these areas will be critical to the success of the current proposal.

Preliminary Data on Approach to Activity Monitoring and Surveillance of Activity. We are currently in the 5th year of an NIH-funded SCCOR randomized trial assessing the effects of exercise training on modifying abdominal aortic aneurysm biology and early disease progression. In the current proposal, similar methods for monitoring and surveillance of physical activity will be employed, which are described below.

RESEARCH DESIGN and METHODS

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 criteria will be considered for the study. Only patients with a good prognosis (annual mortality <1% based on VA multivariate scores (56, 57) will be considered. Patients with left main disease or proximal LAD disease will be excluded. Additional exclusion criteria include those with unstable angina, a history of heart failure (EF ≤30%), pacemakers, atrial fibrillation, myocardial infarction within the last 3 months, *diabetes*, and those with orthopedic problems interfering with the ability to exercise regularly.

Recruitment. *A study flow chart including screening, baseline evaluations, and procedures is presented in Appendix I. Subjects will be recruited from the following populations: 1) patients referred for a clinically-indicated stress myocardial perfusion study (nuclear, echo, or CT); and 2) patients who have a positive exercise test with >1.0 mm ST-segment deviation from baseline on a standard treadmill exercise test, estimated to have a >80% probability of disease based on VA scores (56,57). There are approximately 2,500 patients who undergo these evaluations for CAD at our facility annually, providing a large pool of potential subjects for the study. Potential subjects will be referred for PET/CTA, and baseline PET/CTA findings will confirm patients meet inclusion and exclusion criteria. If the PET/CTA studies show significant ischemia in a moderate to large territory supplied by a significantly diseased vessel, these patients will be recruited for the study.*

PET is considered the gold standard for stress perfusion imaging. Thus, only patients who have moderate to large areas of moderate to severe perfusion defects will be recruited. In addition, only subjects who have a perfusion defect on PET supplied by a significantly diseased artery on CTA will be recruited. Only subjects actually referred for PCI will be considered for the study. A partial waiver of authorization (per HIPAA) will be obtained in order to access medical records or contact individuals for the purpose of study recruitment. A total of 64 subjects will be recruited; randomization will be stratified by age, exercise capacity, and BMI so that these variables will be matched evenly between exercise intervention and PCI groups.

Inclusion of Women and Minorities. The majority of our patient census is male (≈95%), and we expect study enrollment to reflect this gender distribution; however, women will be included if they are eligible. Representatives of all ethnic groups will be included as they are typically represented in the Cardiology clinical service.

Screening Process and Informed Consent. *The study will be discussed with potential subjects by study personnel after direct referral from the study Co-PI (Dr. Froelicher) or from one of the Co-Investigators (Drs. Nguyen, Segall, Giacomini, and Fearon). A chart review will be performed to ensure participants meet inclusion and exclusion criteria and a brief history and questionnaire on demographics and functional status will be completed. If additional tests are needed to confirm presence of any exclusion criteria, they will be done in consultation with the treating physician for that participant. Informed consent will be obtained by study personnel providing sufficient time for decision-making. It is general clinical practice to offer PCI to patients with lesions described above, even though many of these lesions are not associated with high risk. Despite there being no proven benefit with PCI, many physicians and patients often prefer "to do something" and treat these lesions invasively. After carefully explaining to potential subjects that they have a high probability of having CAD and that there is controversy regarding the optimal treatment, only those who agree to randomization for either PCI or exercise intervention will be consented for the study.* Once informed consent is obtained, subjects will undergo a baseline exercise test. They will then be randomized to the exercise group or to PCI and usual care.

Study Procedures

After informed consent is obtained, participants will undergo standard clinical examination and thorough medical history. This evaluation will be used to assure clinical stability and that the

subject meets all inclusion criteria. Along with the baseline exercise test, questionnaires will be administered regarding current and past physical activity patterns, quality of life, and symptoms. Fasting blood labs will be obtained on a different day than the exercise test.

Cardiopulmonary Exercise Testing. Peak VO_2 will be 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. A thorough clinical history, medications and risk factors will be recorded prospectively at the time of baseline exercise testing using computerized forms that include standard definitions of clinical conditions and exercise 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 minutes (58). We previously observed that this protocol provides the closest relation between measured and estimated metabolic equivalents (METs) (59). Patients will be discouraged from using the handrails for support. Medications will not be changed or stopped prior to testing. A 12-lead electrocardiogram, heart rate, and blood pressure responses will be monitored throughout the exercise test and recovery period. Ventilatory gas exchange measurements will be obtained continuously at rest, throughout exercise, and during 5 minutes of recovery. All subjects will be encouraged to give a maximal effort, and the Borg 6-20 scale will be used to quantify subjective effort (60). Standardized clinical indications for stopping will be used. ST-segment depression will be measured visually at the J junction, and slope will be determined over the following 60 ms and classified as upsloping, horizontal, or downsloping. Ventricular tachycardia will be defined as three or more consecutive premature ventricular contractions, and *frequent* premature ventricular contractions will be defined as 10% or more of the total ventricular contractions. Blood pressure will be measured manually, and exercise capacity will be measured directly using ventilatory gas exchange techniques. The exercise tests will be performed, analyzed, and reported according to a standardized protocol and utilizing a computerized database (61).

The Duke Treadmill Score (62) and the VA Prognostic Score (63) will be used to help estimate risk and assess suitability for exercise training. The American Heart Association Guidelines on Exercise Testing (64) 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 HCS and incorporates pre-and post-test responses that have been shown to powerfully estimate risk in Veterans referred for exercise testing (63). 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, more than 1 mm ST depression, paced rhythm) will be excluded. Patients with hemodynamic instability or inability to exercise, those with complicating illnesses or questionable motivation to sustain prolonged training will also be excluded.

Exercise Training. Initially, all subjects will undergo supervised exercise sessions 3 times weekly over a 2 month period. The purpose of these sessions will be 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 provide guidelines and education in terms of what is expected of them during the study. Subjects will then exercise at home, with an in-house exercise session repeated every 2 weeks for the duration of the study. The biweekly exercise sessions will be used 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 American Heart Association, American College of Sports Medicine, and American Association of Cardiovascular and Pulmonary Rehabilitation will be followed (64,65,66). The exercise sessions will 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 will initially be targeted to achieve 60% of heart rate reserve for duration of 30 minutes; exercise intensity will be documented for each patient by frequent (5 minute) recordings of heart rate and

perceived effort. Progression of exercise intensity will be individualized in accordance with established guidelines (ACSM, AACVPR), but in general the goal will be to increase intensity and duration to 70 to 80% heart rate reserve and 45 minutes, respectively. All in-house sessions and activity surveillance will be supervised by exercise physiologists certified by the American College of Sports Medicine (66). Two cardiologists (VF and PN) and a clinical fellow will address patient's clinical concerns as necessary.

During the initial supervised sessions, resistance exercise will involve 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. Subjects will perform 12 to 15 repetitions at 70% of the 5-repitition maximum with a minimum 2-minute rest period between sets. Subjects will gradually increase to 2 sets of these exercises, with increasing resistance as tolerated. Subjects will be given hand-held 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. Thera-Bands are specially designed latex bands used for resistance exercise and have been effectively employed in subjects with CAD.

Home Exercise Training. Subjects will 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 and activity tracking devices (described below). Cycle ergometers will be provided for home use (Stamina 4600, Springfield, MO), but the subjects will be encouraged to achieve an individualized, targeted exercise stimulus using walking, stair stepping, and other available modes of exercise. Activity logs will be given to each patient to record activities, their intensity, and duration, and to document daily pedometer steps; heart rate will be recorded at 5-minute intervals during exercise sessions.

Additional Monitoring of Daily Activities: *In addition to the formal training sessions, subjects will be encouraged to increase their daily activities, including exercising at a moderate but individualized intensity for a minimum of 45 minutes each day they do not exercise at the VA facility.* Activity will be documented by issuing a pedometer (Accusplit AE-180, San Jose, CA), a Polar heart rate monitor (Polar Inc. Kempele, Finland), and an ActiGraph GT1M accelerometer (Sarasota, FL). Using activity counts recorded by the accelerometer, standardized equations will be used to express energy expenditure in kilocalories. This approach is currently being used at our facility for monitoring activity for the aforementioned NIH study (47), and the Co-PI (JM) has extensive experience in monitoring and surveillance of physical activity using these devices. Subjects performing home exercise will return to the hospital monthly for downloading of heart rate/activity data.

Monitoring Phone Calls. For all subjects, follow-up phone calls will be 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. If patients in the exercise group fail to meet previously defined exercise goals, they will be strongly encouraged to increase their activity and monitoring of activities will be increased. Energy costs of activities will be estimated from the ACSM Compendium of Physical Activities (67). Energy expenditure will be expressed in terms of both kcal/week and MET/hours/week.

Subjects in the exercise group will also undergo education and encouragement to increase their daily activities. Patient-oriented educational materials provided by the AHA and CDC will be distributed to all subjects in the exercise group. *Sedentary individuals typically average 1,000 to 3,000 steps/day, and one of our goals will be for the exercise group to gradually increase daily walking on an individualized basis.* Subjects will be given standardized logs to record their steps at the end of each day. During each weekly phone call and each visit to the hospital, staff will record cumulative steps and steps/day and batteries for use with monitoring devices will be

issued as needed. A parallel goal will be to achieve 2,000 kcals/week of energy expenditure based on the VETS 7-Day Recall Questionnaire; this amount is the equivalent of approximately 1 hour 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 (24,31,68).

Blood Panels

Standard blood labs and lipid panels including total cholesterol, LDL, HDL, ApoB, lipoprotein(a), C-reactive protein, fasting glucose, and triglycerides will be determined at *baseline, every 4 months, and at 1 year for both groups.* All analyses will be performed by the VA Clinical Laboratory.

Questionnaires

A synopsis of the questionnaires instruments to be used in the study is presented in Appendix II.

Physical Activity Questionnaires. During screening, physical activity patterns will be quantified in all subjects. Quantification of activity will be performed using the VA Physical Activity Questionnaire (VAPAQ), an instrument that has been used extensively by Drs. Myers and Froelicher over the last 20 years (31). The questionnaire is conducted by an experienced staff member through a detailed interview and takes about 15 minutes. Metabolic costs of occupational and recreational activities will be computed, and energy expenditure will be expressed in kilocalories per week. Energy expenditure will be expressed in terms of lifetime adulthood recreational and occupational activity. Recreational activity will also be expressed separately as energy expended during the year before baseline testing (recent activity).

In addition to the initial VA activity questionnaire, all subjects will record daily activities throughout the study using a daily exercise log (recorded by each subject, Appendix III), and the Veterans Exercise Testing Study 7 Day Activity Recall (recorded weekly by interview with staff member, Appendix IV). The daily logs will record compliance to the exercise regimen and quantify any changes in physical activity that take place during the study.

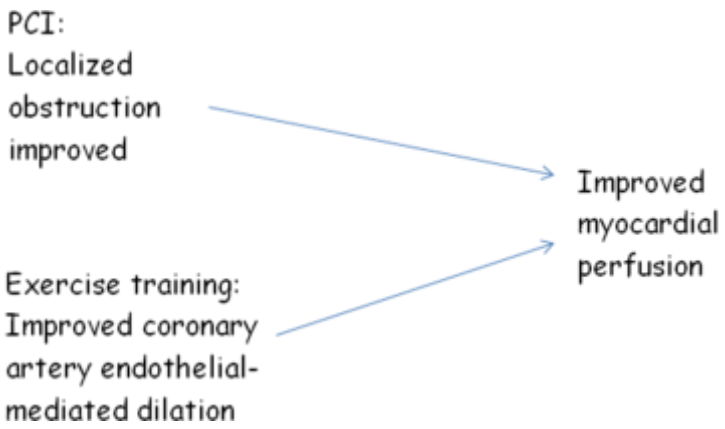
Symptom Questionnaire. Symptom relief is an important outcome associated with both PCI and exercise intervention, and angina symptoms will be monitored closely throughout the study. The Seattle Angina Questionnaire (69) will be used to quantify angina symptoms, and any changes in symptoms, at 3 month intervals. The Seattle Angina Questionnaire was developed and originally validated among veterans. It is a widely validated instrument that measures five clinically important dimensions of health in patients with CAD. It has been shown to be sensitive to clinical change and is considered a reliable instrument for measuring clinical outcomes in patients with CAD.

Quality of Life. Quality of life will be assessed at baseline, 6-months and 1 year using the standard SF-36 questionnaire (70). The SF-36 provides 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. This tool has been used in several thousand clinical studies and has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments.

PET/CTA Study Protocol

Rationale and Accuracy of PET/CTA in the Proposed Study. *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 (see figure), but they have not been previously compared, particularly in a randomized fashion. Myocardial perfusion reserve determined by PET will be the primary outcome measure. It is defined as the ratio of myocardial perfusion during stress to myocardial perfusion at rest. Myocardial perfusion reserve provides information on the functional significance of anatomic stenosis and assesses the ability of the coronary arteries to dilate. It is a well-validated measure of changes in myocardial blood flow both during rest and stress conditions. 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 (64,71,72). Quantification of myocardial perfusion can be performed with chemical (72-76), exercise (77), or psychological (55) stress, and these methods have been employed to study myocardial blood flow by the investigators of the current proposal. While only a year of training is unlikely to demonstrate changes in coronary atheroma obstruction similar to PCI, it has been shown to improve the ability of arteries to dilate very quickly (ie, within weeks).



A global rather than a regional measure is preferred because a regional method could miss the global improvement in myocardial perfusion 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 overall myocardial perfusion and not just the perfusion of the territory supplied by the stenotic artery.

In addition, we have chosen myocardial perfusion reserve measured during hyperemia because previous studies have shown improvements in myocardial perfusion reserve following either exercise training (78) or PCI (79), 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 (19) and myocardial perfusion measured by PET (78). The latter study was a small evaluation of 7 patients using PET perfusion; the investigators reported a 20% improvement in myocardial perfusion reserve after 14 weeks of exercise training. In one study among patients evaluated before and after receiving PCI, a 20% improvement in myocardial perfusion measured by PET was observed (79). 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 slope of the correlation lines have been shown to be 0.98 and 0.96, respectively, with inter- and intra-observer reliabilities of 0.97 (80). The diagnostic accuracy of PET has been reported in many studies; the table below summarizes the accuracy of PET compared with invasive coronary angiography. Note that the weighted summary shows an overall predictive accuracy of 0.90, higher than other non-invasive methods for detecting coronary artery disease.

Previous Studies Assessing the Diagnostic Accuracy of PET

Reference	# patients	PET radiotracer	Sensitivity	Specificity	PPV	NPV	Accuracy
Sampson et al.	102	^{82}Rb	0.93	0.83	0.80	0.94	0.87
Bateman et al.	112	^{82}Rb	0.87	0.93	0.95	0.81	0.89
Marwick et al.	74	^{82}Rb	0.90	1	1	0.36	0.91
Grover-McKay et al.	31	^{82}Rb	1	0.73	0.80	1	0.87
Stewart et al.	81	^{82}Rb	0.83	0.86	0.94	0.64	0.84
Go et al.	202	^{82}Rb	0.93	78	0.93	0.80	0.90
Demer et al.	193	^{82}Rb /^{13}N-am	83	0.95	0.98	0.60	0.85
Tamaki et al.	51	^{13}N-am	0.98	1	1	0.75	0.98
Gould et al.	31	^{82}Rb /^{13}N-am	0.95	1	1	0.90	0.97
Weighted summary	**877**		**0.90**	**0.89**	**0.94**	**0.73**	**0.90**

PPV = positive predictive value; NPV = negative predictive value; ^{82}Rb= rubidium chloride; ^{13}N-am = Ammonia

CTA, commonly performed in conjunction with PET, will be 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) (33). CAC has been shown to be highly reproducible (33), is strongly correlated with angiographic coronary disease (81), and is a powerful predictor of cardiac events independent of other cardiovascular risk factors (82). The combination of PET/CTA provides information that previously could only be obtained invasively using coronary flow wires and invasive x-ray angiography. This will permit a non-invasive way to evaluate both functional and anatomical adaptations to exercise.

PET Methods. A hybrid 64-row PET/CT scanner (GE Discovery VCT, General Electric, WI, USA) will be used in the study. Images will be acquired with simultaneous ECG gating (8 frames/cycle). Heart rate, arterial blood pressure, and 12-lead ECGs will be recorded continuously throughout the evaluation. Heart rate and the arterial blood pressure obtained during the first 2 minutes 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 will be performed at baseline and 1-year in all subjects. Intravenous ^{13}NH3 will be used as the flow tracer and serial imaging with PET will be performed (83,84). Measurements will be performed at baseline, and after pharmacologic stress with dipyridamole (85). A 20-minute transmission scan will be acquired first for correction of photon attenuation (86). After the first intravenous injection of ^{13}NH3 (15 to 20 mCi), resting serial transaxial images will be acquired in a sequence consisting of 12 image frames of 10 seconds, 2 frames of 30 seconds, and 1 frame of 900 seconds. Forty-five minutes later, 0.56 mg/kg of dipyridamole IV will be infused over 4 minutes (85). ^{13}NH3 (15 to 20 mCi) will be injected 4 minutes after the end of the dipyridamole infusion, and serial images will be recorded in the same sequence. Myocardial blood flow at rest and following dipyridamole infusion will be expressed as ml flow/100 g/min. The myocardial perfusion reserve will be calculated as the ratio of the myocardial blood flow during stress (e.g. after dipyridamole) and the myocardial blood flow at rest.

Commercially available software (Emory tool box) will be used to quantitatively analyze PET myocardial perfusion images. Stress and rest images will be divided according to the 17-segment model (87). The software will define whether ischemia is present and the location and extent of the ischemia relative to the specific myocardial territory (88). The software compares normalized relative radiotracer uptake in reconstructed slices against normal data files. Relative radiotracer uptake on PET images is displayed either as polar plots or bull's eye plots, or as circumferential count distribution profiles. The size of myocardial perfusion defects will be expressed as percentage of the left ventricle. In general, defect extent will be 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 will be defined as mild, moderate, or severe based on myocardial tracer content compared against normalized data (89). Qualitative interpretation by Drs. Nguyen and Segall will be used to determine if there were technical issues with regard to processing that impair analysis by the software. *Drs. Nguyen and Segall will oversee all PET/CTA scans and their interpretation, and they will be blinded to study group when reviewing the images.*

CT Imaging. After myocardial perfusion imaging, all patients will undergo calcium scoring and CT angiography (120 kv; 500 mA). First, a prospectively gated low dose sequential CT scan of the heart will be performed for coronary calcium detection and quantification. Patients with pre-scan heart rates above 70 beats per minute will 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 will be administered for coronary dilatation to every patient prior to the scan. ECG-pulsing for radiation dose reduction will be used in all patients. Synchronized to the ECG, CT data sets will be 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 will be used. For post-processing and image interpretation, the images will then transferred to an external designated workstation (Advantage Workstation, GE).

Comparisons of coronary lesions progression or regression of stenosis and change in calcified and noncalicified plaque area) and functional flow reserve between the two groups at baseline and 1 year post-randomization using CT with contrast will be a secondary outcome. For analysis of anatomy (12), a scoring system will 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 will be graded as progression (+1) and a negative difference ≥10% will be graded as regression (-1). Any lesion that necessitates intervention by PCI or bypass surgery will be assigned a grade of +3. Progression from subtotal occlusion to total occlusion (99% to 100%) and spontaneous recanalization will not be graded. In the culprit lesion, an asymptomatic in stent restenosis <50% will be calculated as no change (± 0). An in-stent restenosis of ≥50% will be rated as progression (+1). An in-stent stenosis ≥ 50% that required intervention will be classified as progression (+3). A single variable is calculated per patient by adding the grades assigned to the separate stenosis. For analysis of calcified and non-calcified plaque burden (90), the coronary arteries will be divided into 12 segments according to the American Heart Association classification (33). For every coronary artery segment

(identified via side branches) the presence of calcified or noncalcified plaque, both, or neither will be 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 will be rendered and displayed with a fixed setting (700-HU window, 200-HU level). Plaque areas will be manually traced and volume calculated by multiplying area and slice increment. In the distal segments, analysis of plaque will be limited to the proximal 20 mm. For comparison of calcium scores, total calcium and per artery calcium scores will be compared.

PCI Group

The PCI group will be followed by their cardiologist and will receive usual clinical care. Subjects in both groups will be Veterans who receive their routine care at our facility, so it will be easier to gather pertinent information and to ascertain that subjects in both groups are receiving optimal medical therapy (including blood panels and blood pressure every 4 months). The testing schedule, timelines, and all procedures (except exercise training and PCI) will be similar between the PCI and exercise groups. Physical activity patterns will be monitored in a similar fashion in both the PCI and exercise groups. At each 4 month visit, the Co-PI (Dr. Froelicher) will review the overall adequacy of care for each subject in the study.

Subject Burden

We anticipate that baseline evaluations for each subject will require a total of 2 to 3 hours, with the exercise test and PET/CT evaluations performed on separate days. This will include questionnaires, health history, exercise test and PET/CT evaluations, and blood panel. For the exercise group, the total number of visits to the hospital will be approximately 38 (including exercise training sessions), and for the PCI group the total number of visits will be approximately 8.

Cost Effectiveness Analysis

The cost analysis will examine two research questions in this study:

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

***Estimating Intervention's Costs and Healthcare Expenses*.** The cost identification analysis will be from the provider's (VA's) perspective because of the life-long entitlement of VA services for veterans. We will identify the VA expense to produce the service in each intervention or study arm. Furthermore, 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 will be used (91,92). We have previously used the VA DSS to

evaluate health care costs associated with fitness (25) and physical activity patterns (93). 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.

Intervention's Delivery Expense. We will first 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 will follow the framework proposed by Donaldson (94) where personnel, materials, supplies and space are included in this estimate. To the extent possible, DSS data will be 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.

***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 will be quantified. This will document the appropriate expenses. Base salary and fringe for all personnel involved with the patient will be determined from personnel files. Space required for each encounter will be identified and valued by VA estimates.

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 will be handled by sensitivity analysis and methods consistent with Gold et al. (95). Concerns for patient preferences and a societal estimation are not of concern in this study.

VA Utilization Extractions and Cost-Savings Estimates. Using the VA system (CPRS), we will track 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 will permit 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) will be 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.

Statistical Analysis Plan

Key Question #1: Does exercise training favorably alter coronary anatomy and function as determined by non-invasive imaging techniques?

Statistical Analysis, Key Question #1. Myocardial blood flow using PET at rest and following dipyridamole infusion will be expressed as ml flow/100 g/min. The primary outcome, myocardial perfusion reserve, will be calculated as the ratio of the myocardial blood flow during stress (e.g. after dipyridamole) and the myocardial blood flow at rest. Differences within and between groups will be assessed using repeated measures ANOVA, with group (exercise vs. PCI) and test (baseline vs. 1-year) as factors. Post-hoc procedures will be performed using the Bonferonni method.

Key Question #2: Can a program of exercise therapy improve outcomes (exercise capacity, symptoms, repeat hospitalizations, and quality of life) in patients with CAD that are equivalent or superior to PCI?

Statistical Analysis, Key Question #2. These secondary outcomes will include changes in peak VO_2 and other cardiopulmonary exercise test responses (including VO_2 at the ventilatory threshold, exercise time, and heart rate recovery), quality of life measures, and lipid panels. Paired tests will be used (paired t-test or Wilcoxon signed rank test) to compare continuous variables between groups at baseline. Differences between groups after the 1-year study period will be assessed by repeated measures ANOVA, with group (exercise vs. PCI) and test (baseline vs. 1-year) as factors. Post-hoc procedures will be performed using the Bonferonni method.

Key Question #3: Will exercise training reduce costs as compared to standard PCI after 1-year?

Statistical Analysis, Key Question #3. Comparison of costs will be made for the individual level change scores using the intervention net-costs (intervention delivery minus healthcare expense cost-savings). Cost effectiveness of the intervention will be defined by the primary outcome at the patient level. That is, changes from baseline in individual global myocardial perfusion reserve using PET at 1-year will be used to calculate the effect. Differences in costs between groups will be assessed using ANOVA.

Sample Size Estimates

Sample size estimates are based on our primary endpoint, change in global myocardial blood flow reserve from baseline using pharmacologic stress with dipyridamole, and applying variance in myocardial blood flow reserve measured by PET published previously in subjects with coronary artery disease (71,77,78). We anticipate that the overall change in the primary endpoint will be approximately 15%; this is based on previous measurements of coronary blood flow reserve using PET comparing sedentary and fit subjects cross-sectionally (77), after exercise training (78), and risk reduction interventions such as smoking cessation (96). We also anticipate that these changes will parallel the well-documented changes in exercise capacity with training in subjects with CAD (i.e. mean change in peak $VO_2 \approx 15\%$) (18,19,24). Given a standard deviation of myocardial flow reserve in similar populations of 0.20 ml/g/min both at baseline and after treatment with a pre-post correlation of 0.65 (calculated from the data in reference 96), the standard deviation of the change in myocardial blood flow is 0.167. We want to detect a 15% change (absolute change of 0.15 x 0.9 or 0.135) so the standardized effect size (absolute value of difference in group values for mean change divided by the standard deviation) is about 0.81. Using a 2-sided significance level of 0.05 and 80% power, 25 subjects in each group will be needed to complete the protocol.

We anticipate that there will be a 20% dropout rate, which is typical of that in the cardiac rehabilitation literature and in accordance with our previous experience. Thus, our target enrollment will be 32 subjects in each group. The dropout rate may be lower given that compliance tends to be better in research studies compared to clinical practice, and that the subjects will receive continuous monitoring, follow-up, and encouragement to remain physically active. *Dropouts will not be included in the statistical analyses (97).*

Data Management. All data will be recorded on paper worksheets and entered and maintained in an Access database (Microsoft Corp). This relational database allows storage and manipulation of large data sets and efficient integration of data from multiple sources. Study data will be regularly entered for each participant as they are obtained and error-checking will be performed on an ongoing basis throughout the study. Data will be stored only on VA servers and protected by VA firewalls. Standard security practices will be employed to ensure confidentiality and data integrity. Subject codes will be used in all data files, and identifying information will be kept separately.

Timeline

Identification and recruitment of eligible subjects will take place during the initial months of the study, and exercise training will begin as soon as eligibility is confirmed and baseline testing completed. We anticipate that all subjects will be recruited during the first 1.5 years of the study and that the project will take 3 years to complete. We do not expect much delay in getting started as there is an established exercise training research program at the VA Palo Alto Medical Center. Statistical analyses, reports, and manuscript writing will begin during year 3. An outline of the study timeline and tasks is presented in Appendix V.

Collaboration

All studies will be performed in the Cardiology Division at the Palo Alto VAHCS, where there are laboratories for electrocardiography, echocardiography, and exercise testing currently in use. All training will be performed in the Palo Alto VAHCS Rehabilitation Research & Development Center, on the campus of the Medical Center. The training facility is currently being used for an ongoing NIH SCCOR project ("Exercise Therapy in Abdominal Aortic Aneurysm Disease"), where both dynamic and resistance exercise equipment are in place, and will be used for the current study. All exercise testing and training procedures will be performed by the study personnel; collaboration with the Nuclear Medicine Department will be necessary to perform the PET/CTA scans. Collaboration with the Cardiac Catheterization Laboratory will be necessary to recruit potential subjects for the study. Drs. Froelicher and Nguyen will collaborate with Dr. Myers, the nurse coordinator, and other study personnel to address any clinical concerns that may arise.

Relevant Publications

The Co-PIs have a long history of publication in the areas of exercise testing, training, and epidemiology in patients with cardiovascular disease. Selected publications are listed below:

Books:

Froelicher VF, Myers J. Manual of Exercise Testing, 3rd Edition. St Louis: WB Saunders, 2007.

Froelicher VF, Myers J. Exercise and the Heart: St Louis: WB Saunders, 5th Edition, 2006.

Myers J. Essentials of Cardiopulmonary Exercise Testing. Champaign: Human Kinetics Publishers, 1996.

Book Chapters:

Myers J, Brubaker P. Chronic Heart Failure. In Durstine JL, and Moore G (Eds.), ACSM's Exercise Management for Persons with Chronic Diseases and Disabilities. Champaign: Human Kinetics. 3rd edition, 2009.

Myers J. Exercise and Fitness. In: European Society of Cardiology Textbook on Cardiovascular Prevention and Rehabilitation. Perk J, Mathes (eds.) London: Springer-Verlag, 2007.

Myers J, Froelicher VF. Rehabilitation of the Patient with Cardiovascular Disease. In: Antman EM (ed.) Cardiovascular Therapeutics. Philadelphia: WB Saunders, 2007.

Papers:

Myers J, White J, Dalman R. Effects of exercise training in abdominal aortic aneurism disease: Preliminary results from a randomized trial. J Cardiopulm Rehabil Prev, in press, 2010.

Myers J, Arena R, Franklin B, Pina I, Kraus W, McInnis K, Balady G. Recommendations for Clinical Exercise Laboratories. A Scientific Statement for Healthcare Professionals from the American Heart Association Committee of the Clinical Cardiology Council on Exercise, Cardiac Rehabilitation, and Prevention, and the Council on Nutrition, Physical Activity, and Metabolism. Circulation 119:3144-3161, 2009.

Myers J. Exercise capacity and prognosis in chronic heart failure. Circulation 119:3165-3167, 2009.

Freeman J, Froelicher V, Ashley E. The ageing athlete: screening prior to vigorous exertion in asymptomatic adults without known cardiovascular disease. Br J Sports Med 43:696-701, 2009

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Table 1: Schedule of measurements.

Measurement	Baseline	4 Months	6 Months	8 Months	1-Year
- Vitals, weight & physical exam	√	√	√	√	√
Fasting Bloods					
- Lipid Panel, standard Chem 20	√	√		√	√
- Hemoglobin A1c, CRP	√	√		√	√
Fitness and Functional Capacity					
- Cardiopulmonary Exercise Test	√		√		√
- Strength, Waist/Hip ratio	√		√		√
Myocardial Perfusion					
- PET/CTA	√				√
Questionnaires					
- VA Physical Activity Ques.	√		√		√
- VETS 7-Day Activity Recall*	√	weekly	weekly	weekly	weekly
- Seattle Angina Questionnaire	√		√		√
- SF-36 Quality of Life	√		√		√

* Activity logs will be kept daily throughout the study, with the questionnaire performed weekly