BRIEFING MATERIAL FOR THE

MEDICARE COVERAGE ADVISORY COMMITTEE (MCAC)

REGARDING

PERCUTANEOUS MYOCARDIAL REVASCULARIZATION

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1. Executive Summary

On May 28, 2004, CMS announced its intention to convene the Medicare Coverage Advisory Committee (MCAC) on July 14, 2004, to discuss and provide recommendations regarding the scientific evidence available for Transmyocardial Revascularization (TMR) and Percutaneous Myocardial Revascularization (PMR) as a treatment for severe angina.[Federal Register May 28, 2004] The CardioGenesis TMR system was approved by the Food and Drug Administration (FDA) in 1999 and has received Medicare coverage since 1999. Although available in Canada and the European Union, the CardioGenesis Axcis percutaneous device (or any other percutaneous myocardial revascularization device) has yet received FDA approval and thus is not available in the United States. CardioGenesis has objected, and continues to object, to CMS's direction that the MCAC consider PMR at this time. Such consideration is premature in that the FDA approval process will elicit more data about PMR, and the MCAC should have at least that level of data available to it before being asked to deliberate on coverage issues surrounding PMR.

As detailed in the Federal Register notice and subsequent materials available on the CMS website for this meeting, CMS requires that all materials submitted for consideration contain responses to the specific questions intended for MCAC review. This section of this briefing document provides summary responses to the questions posed by CMS for PMR using the CardioGenesis Axcis PMR System. Due to differences among the various PMR systems, it is not scientifically appropriate to combine them in a single response. Following a background review and overview of the devices, summaries and discussions of the significant clinical trial data supporting these responses are provided. Copies of the peer-reviewed, published literature for the randomized, controlled clinical trials (RCTs) conducted using the CardioGenesis Axcis PMR System are attached.

1. How well does the evidence address the data needed to determine the effectiveness of PMR *using the CardioGenesis Axcis System* in the treatment of chronic, refractory angina in study patients for whom other methods of revascularization are contraindicated?

Three peer-reviewed publications documenting one-year outcomes of randomized, controlled trials using this device, one of which was double blinded, demonstrate a consistency of effect in the relief of chronic refractory, angina in patients who are ineligible for coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Notably, the double-blinded trial was conducted by institutions independent of the manufacturer. These trials further demonstrate consistency in angina-related quality of life using the Seattle Angina Questionnaire, a validated tool recommended for this application.[Spertus 1995] This is consistent with an independent technology assessment recently published by ECRI, a nonprofit health technology assessment information service,[†] which concluded that "PMR plus medical therapy appears to be more effective at reducing angina symptoms and hospitalizations for unstable angina than medical therapy alone." Due to the availability of multiple trial reports, replicating significant benefit in selected patients, the evidence more than moderately addresses the data needed to determine the effectiveness of PMR using this device in the treatment of chronic, refractory angina in study patients for whom other methods of revascularization are contraindicated.

[†]ECRI has been established as an Evidence-based Practice Center (EPC) by the US Department of Health and Human Services, Agency for Healthcare Quality and Research (ARHQ).

2. How confident are you in the validity of the scientific data_for this outcome using the CardioGenesis Axcis system? (no confidence = 1; moderate confidence =3; high confidence = 5); and, how likely is it that PMR using the CardioGenesis Axcis system will improve this outcome (compared to Usual Care) (not likely = 1; reasonably likely = 3; very likely = 5)?

   - Short term mortality: All trials using this device demonstrated a low rate of 30-day mortality (0% to 0.9%) similar to controls (0% to 2.5%). Therefore, there is moderate confidence that PMR using the CardioGenesis Axcis system will not affect this outcome. This is consistent with the findings from the recent ECRI technology assessment information, which concluded that "early and overall mortality rates did not differ significantly between [groups]."
   - Long-term survival: All trials using this device demonstrated similar survival rates at one year (93% to 100%) compared to controls (95% to 97%). One trial (Oesterle 2000) reported a nonsignificantly higher mortality rate in PMR (7.3%) than control patients (2.7%), p=0.12. Compared to one-year mortality rates reported in the literature for randomized medically managed control groups (4% to 17%),[†] this observed rate for the control group appears to be low. Another trial (Salem 2004) reported a nonsignificantly lower mortality rate in PMR (0.0%) than control patients (4.8%), p=0.17. Therefore, there is low to moderate confidence that PMR using the CardioGenesis Axcis system will affect this outcome.
   - Morbidity: All trials using this device demonstrated similar rates of adverse events at one year compared to controls. The largest trial [Oesterle 2000] demonstrated that hospitalizations for angina were markedly reduced in the PMR group compared to the medical therapy group. Furthermore, angina class is a key indicator of patient morbidity.

[†]Allen 1999, Burkhoff 1999, Frazier 1999, Schofield 1999, Aaberge 2000, Gray 2003, Salem 2004.

All the RCTs showed a statistically significant improvement of ≥2 angina classes in PMR relative to control patients at one year. Therefore, there is moderate confidence that PMR using the CardioGenesis Axcis system will more than likely improve this outcome.

- Quality of Life: All trials using this device demonstrated significantly better angina-related quality of life using the validated SAQ tool in PMR patients compared to controls. This is consistent with the substantial angina improvement observed in unblinded and blinded trials.

3. How confident are you that PMR using the CardioGenesis Axcis system will produce a clinically important net health benefit in the treatment of chronic, refractory angina in study patients for whom other methods of revascularization are contraindicated (no confidence = 1; moderate confidence =3; high confidence = 5)?

In patients with medically refractory angina for whom PCI or CABG are not an option, angina relief and associated quality of life improvement is a clinically important health benefit. Given the details in items (1) and (2) above, there is more than moderate confidence that PMR using the CardioGenesis Axcis system will produce a clinically important net health benefit in selected patients.

4. Based on the literature presented, how likely is it that the results of PMR using the CardioGenesis Axcis system in the treatment of chronic, medically refractory angina can be generalized to the Medicare population and facilities/physicians in community practice (not likely = 1; reasonably likely = 3; very likely = 5)?

- Medicare population: PMR using the CardioGenesis Axcis system is intended for patients with medically refractory angina. The average age of the patients studied in the randomized clinical trials was between 62 and 67 years. Therefore, based on the average age of study patients and the range of patients enrolled in the studies, the evidence from these studies can be generalized to Medicare patients.

- Facilities/physicians in community practice: The only physicians who have used the CardioGenesis Axcis system are trained interventional cardiologists. Within the US, these physicians have utilized this system under an approved investigational device exemption (IDE); however, this has not been available to physicians in community practice because this device is not approved by the US FDA. CardioGenesis has proposed a rigorous training program, which is utilized outside the US where this device is available. Based on the level of training and skill of interventional cardiologists and the required PMR training program prior instituting the procedure, the technique is generalizable to interventional cardiologists in community practice, following FDA approval.

2. Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CABG	coronary artery bypass grafting
CCS	Canadian Cardiovascular Society
CMS	Centers for Medicare and Medicaid Services
ECG	electrocardiography
ECRI	Emergency Care Research Institute
DASI	Duke activity status index
FDA	Food and Drug Administration
Ho:YAG	holmium:yttrium-aluminum-garnet
MCAC	Medicare Coverage Advisory Committee
PCI	percutaneous coronary intervention
PMR	percutaneous myocardial revascularization
RCTs	randomized, controlled clinical trials
SAQ	Seattle angina questionnaire
TMR	transmyocardial laser revascularization
Xe:Cl	xenon excimer chloride

3. Background

Less invasive techniques for the delivery of laser myocardial revascularization have been or are under development using fiberoptic, catheter-based technologies.[Kim 1997] Although both holmium:yttrium-aluminum-garnet (Ho:YAG) and xenon excimer chloride (Xe:Cl) laser energy can be delivered via fiberoptics, peer-reviewed results from multicenter randomized, controlled clinical trials (RCTs) using a percutaneous system have been published using only two Ho:YAG systems. No percutaneous system has received U.S. FDA approval. Because any product regulated by the FDA must receive FDA approval for at least one indication to be eligible for Medicare coverage, no percutaneous system is or has been covered by CMS.[CMS 2004]

In contrast to the surgical approach of TMR, percutaneous myocardial revascularization cannot be delivered under direct visualization; fluoroscopic or other mapping/imaging modality is required. The laser is activated from the endocardial surface. In addition, as illustrated in the randomized controlled trials completed to date, substantially fewer channels are typically placed percutaneously (mean 15 to 20) compared to the number placed during TMR (mean 25 to 45). Because no experimental or clinical studies have compared a TMR system with any percutaneous system, a relationship between TMR and PMR has not been established.

4. Overview

A summary of the literature available for the various percutaneous approaches and systems is reviewed in this section.

Clinical study and/or trial reports involving three different percutaneous laser and delivery systems are available in the literature. Although each system uses a Ho:YAG energy source, the laser parameters and fiberoptic catheter-based delivery systems are different:

- *CardioGenesis PMR System (CardioGenesis Corporation)*: This two catheter coaxial delivery system uses fluoroscopic guidance and tracking to position the laser catheter at targeted regions of the myocardium, and advance the fiber optic tip into the myocardium, creating a partial thickness laser channel. This system is designed to deliver four ECG-synchronized laser pulses through a 1.6-mm fiberoptic lens to create approximately 1mm diameter ablated channels. Advancement of the fiberoptic lens 3mm into the myocardium creates ablated channels that penetrate to a total channel depth of 5 to 6mm. Nonrandomized study reports [Oesterle 1999; Lauer 2000; Kluge 2000], randomized, medically controlled trial reports with one year follow-up [Oesterle 2000/Myers 2002, Gray 2003] and a randomized, double blinded trial report with one year follow-up [Salem 2004] are available in the peer-reviewed literature. All studies were conducted in CCS Class III/IV no option patients, with the majority being in Class III.

- *Eclipse PMR System (Eclipse Surgical Technologies, Inc.)*: This two catheter delivery system uses fluoroscopic guidance and tracking to position the deflectable guide catheter at targeted regions of the myocardium, and advance the fibertoptic tip into the myocardium, creating a partial thickness laser channel. This system is designed to deliver three nonsynchronized laser pulses through a 1-mm multi-fiber bundle to create approximately 1mm diameter ablated channels. Advancement of the fiberoptic tip 3mm into the myocardium creates ablated channels that penetrate to a total depth of 5 to 6mm. Two nonrandomized study reports [Kaul 1999; Shawl 1999] and one randomized, medically controlled trial report with one year follow-up [Whitlow 2003] in no option patients are available in the literature. One six-month feasibility report in PCI-eligible patients [Stone 2001], and a six-month randomized study report of patients with a bypass-eligible chronic total occlusion [Stone 2002] are also available. All studies were conducted in Class III/IV patients, with the majority being in Class III.

- *Biosense DMR System (Biosense Webster)*: The Biosense Webster Direct Myocardial Revascularization (DMR) system is also a Ho: YAG percutaneous myocardial revascularization system. However, this system utilizes a single catheter delivery system, with the 300-μm fiber embedded in the deflectable mapping/positioning catheter. This system delivers a single pulse of ECG-synchronized energy from the surface of the endocardium. Unlike the previous two systems, there is no mechanical advancement of the system into myocardium. This was by design, as this approach was intended to "minimize tissue damage, with less concern for channel formation and greater emphasis on triggering endogenous responses".[Kornowski 2000] The area of ablation for the DMR system on the surface of the tissue is 80% smaller than the CardioGenesis Axcis PMR system.[Salem 2004] Three nonrandomized study reports have appeared in the literature.[Kornowski 2001; Laham 2002; Strehblow 2003] Studies were conducted in Class III/IV patients, with the majority being in Class III. Although a single blinded, randomized trial was conducted, no peer-reviewed final report is available in the literature.

4.1. CardioGenesis Percutaneous System: Studies and RCTs in No Option Patients

More than 450 patients have been studied in published nonrandomized studies and RCTs using this device system and approach. In multiple RCTs, including one using a double-blinded sham-controlled design, statistically and clinically significant results were observed through one year, demonstrating the relief of medically refractory angina and improvement in quality of life in patients for whom PCI and CABG are not an option. A summary of the nonrandomized studies, followed by the RCTs, is provided as follows.

Oesterle (N=30) and Lauer (N=34), reporting feasibility studies in no option patients at several centers in Germany and the US, identified the reasonable safety and initial angina relief and exercise improvement

outcomes of the device at six months.[Oesterle 1999, Lauer 2000] Kluge and associates, evaluating 36 consecutive patients one year post-treatment using rest and stress thallium scintigraphy, reported no changes in rest studies. These authors reported however that regional myocardial flow reserve improved in laser-treated wall segments having initially severely reduced stress perfusion.[Kluge 2000]

The first prospective, multicenter RCT (N=221) conducted with this device was reported by Oesterle and associates. In this trial, investigators assigned patients (median age: 62 years) who were determined to be unsuitable for conventional revascularization and had medically refractory angina (61% Class III; 39% Class IV), evidence of reversible ischemia, ejection fraction ≥30%, and myocardial wall thickness ≥8 mm in target areas to PMR with continued optimal medical management (N=110) or to optimal medical management alone (MM, N=111) and followed patients through one year. Patients with unstable angina requiring hospitalization within 14 days of enrollment were excluded from the trial. The primary endpoints were improvement in CCS functional class and exercise time. Secondary assessments were medication usage, quality of life and adverse events. A mean of 16 channels were placed per patient. There were no procedural deaths, and 30-day mortality was the same in each group (0.9%). Significantly improved outcomes were observed in the PMR group compared to the MM group through one year in terms of ≥2-class angina improvement (46% vs. 11%, $p<0.0001$). A blinded, independent assessment of angina class was also conducted at one year. Although investigators assigned lower angina scores to PMR patients than did the blinded assessor, one year improvement using only the blinded assessment scores were still significantly superior in the PMR vs. MM group ($p=0.002$). Median modified Bruce exercise time improvement as assessed by a blinded exercise core lab was significantly higher in PMR treated patients (89 sec vs. 13 sec, $p=0.008$), as was quality of life per the five components of

the Seattle Angina Questionnaire (SAQ, $p<0.05$). In an exercise-based evaluation of the randomized patients at one year, the blinded exercise core lab determined no increase in the incidence of silent ischemia in the PMR-treated group compared to the MM group (5.7% vs. 5.4%).[Myers 2002] A total of 11 patients died during the 1-year follow-up period (7% PMR, 2.7% MM; $p = 0.12$).

Gray and associates [Gray 2003] reported one-year outcomes from a single-center UK trial that randomized 73 patients (median age: 62 years) who were determined to be unsuitable for conventional revascularization and had medically refractory angina (67% Class III; 33% Class IV), evidence of reversible ischemia, ejection fraction ≥25%, and myocardial wall thickness ≥8 mm in target areas to PMR with continued optimal medical management (N=36) or to optimal medical management alone (MM, N=37) and followed patients through one year; 21 of those patients were included also in the Oesterle report. Patients with unstable angina requiring hospitalization within 14 days of enrollment were excluded from the trial. The primary endpoints were angina improvement and improvement in exercise time. Secondary assessments included medication usage, quality of life and adverse events. A mean of 15 channels were placed per patient. There were no procedural deaths. Significantly improved outcomes were observed in the PMR group compared to the MM group through on year in terms of ≥2-class angina improvement (36% vs. 0%, $p<0.01$); mean modified Bruce exercise time improvement (109 sec vs. -62 sec, $p<0.01$) as assessed by the core laboratory, and angina-related quality of life per the SAQ ($p<0.05$). There was one death in each group at one year (p=ns).

Salem and colleagues at two centers in Norway reported one-year results of a triple blinded (i.e., blinding of patients, treating physicians, and independent assessors) RCT trial, which was conducted under a grant from the Bergen Heart Foundation (Bergen, Norway). A total of 82

patients (mean age: 66 years) who were determined to be unsuitable for conventional revascularization and had had medically refractory angina (87% Class III; 13% Class IV), evidence of reversible ischemia, ejection fraction ≥25%, and myocardial wall thickness ≥8 mm in target areas were randomized to PMR with optimal medical management (N=40) or to a sham procedure with optimal medical management (N=42). The authors state that "the sample size calculation reflects a balance between the need to limit patient exposure to potential hazards from a sham procedure while producing the opportunity for a statistically and clinically justifiable result". Patients with unstable angina requiring hospitalization within 14 days of enrollment were excluded from the trial. The primary endpoint for which the study was designed was improvement in CCS functional class. Secondary assessments were medication usage, quality of life, exercise time, and adverse events. Procedural characteristics between the two groups were similar, with a mean of 19 PMR channels and 20 'sham channels' placed. There were no procedural deaths in the PMR group, and one procedural death in the sham group due to acute myocardial infarction. Excellent primary endpoint follow-up (96%) was obtained at one year. Significant angina improvement in the PMR treated group when compared to the Sham group (≥2-classes, intent to treat analysis) was reported at one year (35% vs. 15%, p=0.04). Angina-related SAQ quality of life scores at one year were significantly higher in PMR than sham patients (p<0.05) although other SAQ components were not different. There was no significant difference in exercise duration between the two groups. There were no deaths in the PMR group and two deaths in the sham group at one year (0% vs. 4.8%, p=0.17).

4.2 Eclipse Percutaneous System: Studies and RCTs in No Option Patients

Shawl (N=27) and Kaul (N=35), reporting feasibility studies in no option patients receiving a mean of 15 channels at several centers in India and

one center in the US, identified the reasonable safety and initial angina relief outcomes of the device at six months compared to baseline.[Shawl 1999; Kaul 1999] Guzzetti and associates reported six-month outcomes from 32 nonrandomized patients at a single Italian center who received a mean of 9 PMR channels using the device. No mortality occurred in the study. Significant improvements in angina class and time to 1mm ST segment depression were observed, however scintigraphic perfusion imaging studies and autonomic nervous system testing showed no changes.

The first RCT (N=330) conducted with this device was reported by Whitlow and associates. In this trial, investigators assigned patients with Class III or IV refractory angina (65% Class III) and reversible perfusion defects on thallium stress testing, ejection fraction of ≥25%, and myocardial wall thickness ≥9 mm to either PMR with continued medical management (N=164) or to medical management alone (MM, N=166) and followed patients through one year.[Whitlow, 2003] Patients with unstable angina requiring hospitalization within 14 days of enrollment were excluded from the trial. A mean of 19 channels were placed per PMR patient. There was one procedural death due to tamponade secondary to a pericardial perforation. Blinded independent assessors performed all evaluations. Significantly improved outcomes were observed in the PMR group compared to the MM group through one year in terms of: ≥2-class angina improvement (38% vs. 19%, p=0.001); mean Naughton exercise time improvement (100 sec vs. -20 sec, p=0.008); and, quality of life according to the Duke Activity Status Index (DASI, p=0.005), as also reflected in the increased freedom from death, myocardial infarction and revascularization attempt (p=0.03) in PMR compared to MM patients. One-year mortality was similar between groups (7.9% vs. 6.7%, PMR vs. MM, p=ns)

4.3 Eclipse Percutaneous System: Studies and RCTs in PCI- or CABG-Eligible Patients

Stone and associates reported the six-month results of a feasibility study conducted in 26 PCI-eligible patients who had coronary lesions that were at high risk for restenosis. Following PCI (angioplasty [96%], stenting [42%], atherectomy [19%]) of the target vessel, a mean of 17 PMR channels were placed in the myocardial area subtended by that vessel.[Stone 2001] Mortality at 30 days and six months was 12% and 19%, respectively. Restenosis in the target vessel occurred in 19% of patients at six months.

Stone later reported the results of a prospective, multicenter, RCT of PMR in patients with a nonrecanalizable chronic total occlusion.[Stone, 2002] *Unfortunately, this study is severely limited in that it was terminated early (at six months, planned for one year) and only 50% follow-up data were obtained at six months, as reconfirmed by co-investigators.[Stone 2002, Perin 2002]* A total of 141 patients with Class III or IV angina and a nonrecanalizable chronic total occlusion having a visible lumen possibly amenable to CABG were randomized to either PMR (N=70) or to continued medical therapy (N=71). Randomization took place after an unsuccessful attempt to cross the chronic total occlusion. Although patients were not informed of their treatment, medically managed patients did not undergo the 30-minute PMR procedure; moreover, patients are consciously sedated during the procedure and as such, patient blinding was not complete.[Perin 2002] A significant difference was not detected between groups in the primary endpoint (exercise time), however the very poor quality of the follow-up in this study limits the scientific validity of the results and therefore, no robust conclusions can be drawn from the outcomes.

4.4 Biosense Percutaneous System: Studies in No Option Patients

Kornowski and associates reported six-month outcomes from 76 nonrandomized patients who were received a mean of 26 DMR channels using the Biosense Webster DMR device. No mortality occurred in the study. Exercise duration was evaluated in 70% of patients (although the test protocol was not identified) and increased by 78 seconds at six months. Dual isotope nuclear perfusion imaging studies showed no changes. Laham and colleagues reported six-month results from 15 nonrandomized patients who received a mean of 32 DMR channels. No mortality occurred. Exercise time increased significantly ($p=0.04$), however angina class nonsignificantly improved to a mean class of 2.5. Nuclear perfusion imaging scans showed no changes, but magnetic resonance imaging showed regional wall thickening and improved motion in treated areas. At a single center in Austria, Strehblow reported significantly improved angina class at 7±4 months in 10 patients treated with the DMR device and in 15 patients treated with the CardioGenesis device, with one death in each group during follow-up.

The methods and results of the blinded, randomized, controlled trial conducted with this device have not been published in a peer-reviewed journal article.

5. Clinical Assessments

An independent technical assessment of the peer-reviewed, published randomized clinical trials, has been published by the Emergency Care Research Institute.[ECRI 2004] This assessment considered only the CardioGenesis Axcis device and the Eclipse PMR device, excluding the Biosense device due to the fact that no peer-reviewed results from a randomized controlled trial using the device has been published, and due to the fact that the manufacturer discontinued the device due to the negative results. ECRI concluded that "PMR

plus medical therapy appears to be more effective at reducing angina symptoms and hospitalizations for unstable angina than medical therapy alone", and "early and overall mortality rates did not differ significantly between [groups]."

In conjunction with the ongoing FDA review process, CardioGenesis commissioned a review of the clinical safety and effectiveness data for the CardioGenesis Axcis PMR System by an expert Medical Review Board, consisting of board-certified physicians and expert statisticians who were not involved in the CardioGenesis PMR trials, and two trialists (*).

The composition of the board was as follows:

- Richard Popp, MD
  Professor, Cardiovascular Medicine, Director of Ethics and Policy, Program of Biodesign, Stanford University; Past President, American College of Cardiology.
- Eric Topol, MD
  Chairman, Dept of Cardiovascular Medicine, Cleveland Clinic Foundation
- Larry Dean, MD*
  Professor of Medicine and Director, Heart Center, University of Washington
- George Abela, MD
  Chief of Cardiology, Michigan St University
- Jan Erik Nordrehaug, MD, PhD*
  Professor of Medicine and Chief of Cardiology, University of Bergen
- Keith B. Allen, MD
  Cardiothoracic Surgeon, Indiana Heart Center
- Stephen Piantadosi, MD, PhD
  Director of Biostatistics and Professor of Oncology, Johns Hopkins Oncology Center; and, Professor of Epidemiology and Biostatistics Johns Hopkins University School of Hygiene and Public Health
- Joel Verter, PhD
  Senior Investigator, Statistics Collaborative, Inc.

This group of experts recognized that patients having severe, medically refractory angina and who are not candidates for CABG or PCI currently have available to them surgical transmyocardial revascularization, an FDA-approved and reimbursed technology. Further, the precise mechanism of action using

either technology is not known, nor is a relationship between PMR using the CardioGenesis Axcis system and TMR. Nonetheless, it is appropriate to evaluate the outcomes in carefully selected patients following treatment with the Axcis device. The board concluded that sufficient reliable data is available to support the conclusion that the Axcis PMR System is safe and effective as labeled for relieving anginal symptoms in patients with medically-refractory angina (CCS Class III or IV) who are not candidates for conventional methods of revascularization (i.e., CABG or PTCA).

6. AHRQ Assessment

An assessment of percutaneous myocardial revascularization was recently posted on the CMS website for consideration by the MCAC panel. This assessment was prepared by the Duke Center for Clinical Health Policy Research and Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ).[AHRQ 2004] In reviewing this assessment, significant concerns have come to light, a summary of which is provided as follows.

- The differences in percutaneous device designs and treatment methods are not disclosed. On page 9 it is indicated that the "typical PMR probe channel measures 5-6mm deep in walls of at least 8mm thickness [Saririan 2003]." This statement, extracted from a review article and not a source publication on any of the devices, is incorrect. Please refer to an accurate discussion [Salem 2004], where the differences in designs between the Axcis and Biosense devices and methods are disclosed. In contrast to the Axcis device and method, the Biosense device uses "no endocardial puncture or channel ablation, 1 pulse, 80% smaller laser spot size". This section of the assessment, therefore, is inaccurate by omission.
- The assessment states that its aim was to "[r]eview the peer-reviewed literature on the outcomes associated with the use of PMR." The methods and results of the blinded trial for the Biosense device have not appeared in a peer-reviewed journal article. Moreover, the assessment acknowledges

that the quality of this study cannot be determined, due to the lack of information. As such, the summary prepared cannot be considered to be accurate and thus cannot be scientifically evaluated in the assessment of PMR. By contrast, ECRI, in their recent assessment of PMR, in fact reviewed only peer-reviewed literature. It should be noted that ECRI is an AHRQ Evidence-based Practice Center.

This raises the issue of selection bias. Whereas a summary of the unpublished study conducted with the Biosense device is provided based on a set of powerpoint slides available on the internet, the one-year results of the randomized controlled trial conducted by Frazier and colleagues evaluating adjunctive TMR in high-risk patients who would be incompletely revascularized by CABG alone are not mentioned. Like the Biosense results, these results also have not been published in a peer-reviewed article, but have been presented.[Frazier 1999]

- The summary of the double blind trial on the CardioGenesis Axcis system [Salem 2004] is inaccurate, both in terms of the methods and the data reported. Please see the summary in this briefing document and the attached published manuscript for an accurate representation.
- The summary of the publication using the Eclipse PMR device in CABG-eligible patients with a chronic total occlusion is inaccurate by omission.[Stone 2002] This study was terminated early, at six months, and accomplished only 50% follow-up at that time. This is a substantial flaw in the study methodology. More complete and 1-year follow-up is critical to assessing validity of outcomes.
- The summary of the publication by Whitlow and colleagues does not disclose the blinding of assessors who evaluated angina class and exercise time throughout the trial.[Whitlow 2003] Disclosure of such controls in a trial is important to accurately evaluate the validity of study outcomes.

7. References

References for the CardioGenesis Axcis System, shown in bold, are attached.

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Attachment 1.

Oesterle SN, Sanborn TA, Ali N, et al. Percutaneous transmyocardial laser revascularisation for severe angina: the PACIFIC randomised trial.

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Articles

Percutaneous transmyocardial laser revascularisation for severe angina: the PACIFIC randomised trial

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Summary

Background Percutaneous transmyocardial laser revascularisation (PTMR) is a proposed catheter-based therapy for refractory angina pectoris when bypass surgery or angioplasty is not possible. We undertook a randomised trial to assess the safety and efficacy of this technique.

Methods 221 patients with reversible ischaemia of Canadian Cardiovascular Society angina class III (61%) or IV (39%) and incomplete response to other therapies were recruited from 13 centres. Patients were randomly assigned PTMR with a holmium:YAG laser plus continued medical treatment (n=110) or continued medical treatment only (n=111). The primary endpoint was the exercise tolerance at 12 months. Analyses were by intention to treat.

Findings 11 patients died and 19 withdrew; 92 PTMR-group and 99 medical-treatment-group patients completed the study. Exercise tolerance at 12 months had increased by a median of 89·0 s (IQR −15 to 183) with PTMR compared with 12·5 s (−67 to 125) with medical treatment only (p=0·008). On masked assessment, angina class was II or lower in 34·1% of PTMR patients compared with 13·0% of those medically treated. All indices of the Seattle angina questionnaire improved more with PTMR than with medical care only. By 12 months there had been eight deaths in the PTMR group and three in the medical treatment group, with similar survival in the two groups.

Interpretation PTMR was associated with increased exercise tolerance time, low morbidity, lower angina scores assessed by masked reviewers, and improved quality of life. Although there is controversy about the mechanism of action, and the contribution of the placebo effect cannot be quantified, this unmasked study suggests that this palliative procedure provides some clinical benefits in the defined population of patients.

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Introduction

Diffuse coronary disease limits surgical and angioplasty options for many patients with severe angina. Transmyocardial laser revascularisation (TMR),[1] a novel strategy for these patients, was recently approved as a palliative procedure by the US Food and Drug Administration. Via thoracotomy, hand-held laser probes are used to create multiple transmyocardial channels in areas of ischaemia. Randomised studies of TMR have shown relief of angina[2-5] and improvement in exercise tolerance.[3] Although the mechanisms of action are not fully understood, stimulation of angiogenesis[6] and regional myocardial denervation[7,8] have been proposed as contributing factors.

The surgical TMR procedure has been adapted to a less invasive catheter-based approach—percutaneous transmyocardial laser revascularisation (PTMR).[9] In this randomised trial in patients with severe angina, the primary hypothesis was that PTMR with continued maximum medical therapy would result in improved exercise tolerance at 1-year follow-up compared with continued medical therapy alone.

Methods

Patients

Patients were recruited from 12 US centres and one UK centre. All sites had approval from local institutional review boards or ethics committees. The medical history was reviewed, an angiogram was done within 3 months to assess eligibility, informed consent was obtained, and the patient underwent baseline testing, which included an echocardiogram, dipyridamole thallium stress test, treadmill exercise tolerance testing (modified Bruce protocol tests) and a self-administered Seattle angina questionnaire.[10] All baseline testing was completed within 3 months of randomisation. Eligible patients had to have: angina of class III or IV on the Canadian Cardiovascular Society scale despite maximum tolerated doses of at least two antianginal drugs; a left-ventricular ejection fraction of 30% or more; and reversible perfusion defects on the thallium stress test. The baseline exercise-testing protocol was designed to provide evidence that each participant's angina was refractory to medical therapy, to account for possible exercise habituation effects, and to ensure test consistency. Prescribed cardiovascular medications were continued before the exercise tolerance test. To be eligible for the study, patients had to have two consecutive exercise-tolerance tests (of a maximum of four tests) with durations within 15% of each other and typical angina during at least one of the qualifying tests.

Major exclusion criteria were: ejection fraction less than 30%; exercise tolerance not limited by angina, symptomatic heart failure; treatment with more than 80 mg furosemide daily (or equivalent dose of another diuretic); left-ventricular wall thickness less than 8 mm (by echocardiography) in the region targeted for PTMR; renal insufficiency (serum creatinine >177 μmol/L);

Characteristic	PTMR plus medical treatment (n=110)	Medical treatment only (n=111)
Demography		
Median (range) age in years	62 (39–83)	62 (38–90)
Male/female	93 (85%)/17 (15%)	97 (87%)/14 (13%)
History		
Diabetes	53 (48%)	46 (41%)
Hypertension	75 (68%)	84 (76%)
Hyperlipidaemia	78 (71%)	94 (85%)
History of smoking		
None	31 (28%)	26 (23%)
Current	15 (14%)	13 (12%)
Former	64 (58%)	72 (65%)
Family history of CAD	70 (64%)	86 (77%)
Previous MI	71 (65%)	76 (68%)
Previous interventions		
None	15 (14%)	4 (4%)
CABG only	41 (37%)	44 (40%)
PTCA only	9 (8%)	7 (6%)
CABG and PTCA	45 (41%)	56 (50%)
Median (range) ejection fraction as %	50 (30–83)	50 (33–79)
Dipyridamole thallium stress test*		
Fixed defects	0 (0–11)	0 (0–10)
Reversible defects	6 (1–12)	5 (1–14)
Angina class		
III	66 (60%)	69 (62%)
IV	44 (40%)	42 (38%)
Median (range) exercise tolerance (s)	443 (34–835)	385 (34–913)
Median (range) SAQ index	38·3 (6·7–86·6)	42·6 (6·3–84·8)

Data are number of participants unless otherwise stated. CAD=coronary-artery disease; MI=myocardial infarction; SAQ=Seattle angina questionnaire.
*Median (range) number of segments affected out of 14; data available for all patients.

Table 1: **Baseline characteristics of patients**

aortic stenosis (valve area <1·5 cm²); severe peripheral vascular disease; evidence of left-ventricular thrombus; clinically significant ventricular arrhythmias; unstable angina (angina at rest requiring intravenous glyceryl trinitrate and anticoagulation); need for adjustment of antianginal medications within 2 weeks of screening; transmural myocardial infarction within 3 months; and non-transmural infarction within 6 weeks of study entry.

Design and procedures

The PACIFIC (Potential Angina Class Improvement From Intramyocardial Channels) study was a prospective, randomised, multicentre trial that compared treatment with the Axcis PTMR system (Eclipse Surgical Technologies, Inc, Sunnyvale, CA, USA) plus continued medical therapy with continued medical therapy alone. The primary endpoint of the study was a change in exercise tolerance at 1-year follow-up. For each study site, participants were randomised within blocks. The block size was variable depending on the number of patients entered for that particular site. After checking a patient's eligibility, the investigator contacted the data-coordinating centre by telephone to obtain a randomisation assignment. Randomisation assignments were retained only at the data-coordinating centre, which was remote from all investigative sites and core laboratories. The randomisation code was revealed at the end of the study after all data had been entered into the database.

Each investigator was instructed in the technique of PTMR,[9] received training on at least two animals, and treated between three and eight patients (non-randomised, run-in phase, n=75) as part of training. Results from these patients were not included in the analysis of the PACIFIC trial.

For PTMR, the patient was sedated and given anticoagulant treatment (heparin to achieve an activated clotting time of about 250 s). Biplane ventriculography and coronary angiography (orthogonal views) were carried out and archived to provide landmarks for tip placement during PTMR. A transparent acetate sheet was fixed over the fluoroscopic monitors, and end-diastolic images of the coronary anatomy and ventricular silhouette were traced; movement of the patient or table was avoided during the procedure. The Axcis PTMR system is a 9 F coaxial catheter system for positioning an optical fibre coupled to a holmium:YAG laser. The optical fibre was capped with a 1·75 mm lens and four nitinol petals to retard advancement through the full thickness of the myocardium during laser activation. The position of each laser channel (created with four laser pulses of 2 J) was also marked on the acetate sheets to ensure that channels were placed at least 1 cm apart. Preclinical testing validated acceptable precision of this technique for placing laser channels.[9]

Patients assigned to the PTMR group were admitted to hospital for overnight observation, serial measurement of cardiac enzyme activities, and a transthoracic echocardiogram. Antianginal drugs were continued in all participants, with doses adjusted only as needed to relieve symptoms while keeping side-effects to a minimum. Patients in both groups were assessed at 3 months, 6 months, and 12 months by angina class (unmasked), exercise tolerance, and Seattle angina questionnaire. Echocardiography was done at 3 months. At 12 months, trained interviewers, unaware of treatment group, telephoned each participant and completed a questionnaire. The answers were reviewed by an independent cardiologist who assigned a class according to the Canadian Cardiovascular Society scale. Core laboratories were used to review results of exercise-tolerance testing, echocardiography, and the angina questionnaire.

Statistics

The primary endpoint was an assessment of increase in exercise duration at 12 months compared with baseline. A sample size of 98 patients per group was based on the ability to detect improvements of 60 s in exercise duration after PTMR compared with no change in the medically treated group, with a power of 0·80 at p=0·05. The SD of the change in exercise duration was assumed to be 150 s from a previous study of TMR.[3] The number of participants was increased to 110 per group to allow for loss to follow-up of up to 10%.

Some patients from both randomised groups (n=24) underwent coronary-artery bypass grafting (CABG) or percutaneous transluminal coronary angiography (PTCA) during follow-up. Data for the whole study were analysed both by intention to treat and after exclusion of these patients.

Baseline characteristics were compared by use of Fisher's exact test (dichotomous data), the Mantel-Haenszel χ^2 test (ordered categorical data), or Wilcoxon's test (continuous data) as appropriate. Survival curves were estimated by the Kaplan-Meier procedure; survival differences between groups were compared by the log-rank test. Changes from baseline in exercise duration, Seattle angina questionnaire index, and ejection fraction were compared between treatment groups by Wilcoxon's test. These changes were measured as the 12-month value minus the baseline value for each variable. The Mantel-Haenszel test was used to compare the distribution of angina scores at 12 months in the treatment groups. Within-group change in ejection fraction from baseline to 3 months was assessed by the signed-rank test. All p values are two-sided.

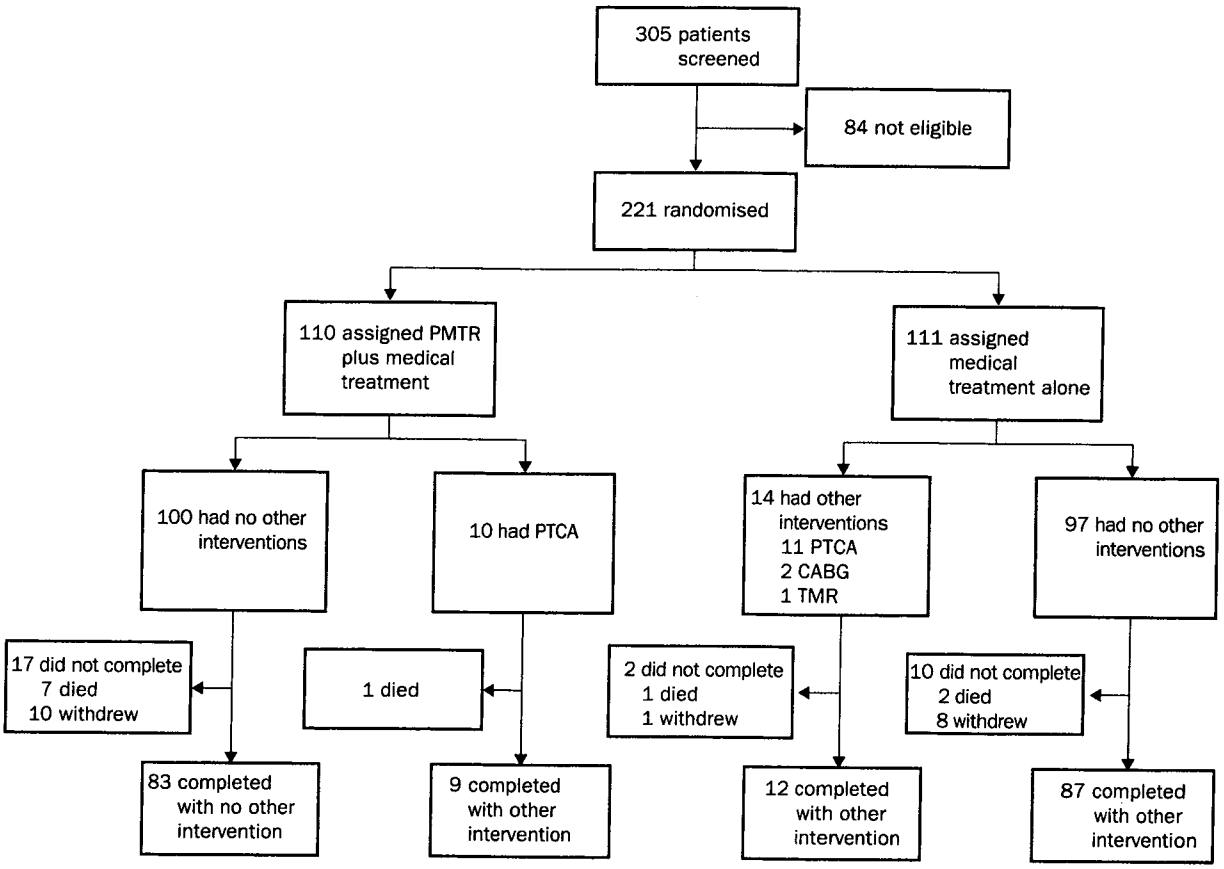


Figure 1: **Trial profile**

Results

75 patients (mean age 60 years [SD 10]) were treated during the run-in phase. Four died during 1-year follow-up and ten underwent either CABG or PTCA for continued angina. Other major adverse advents included one periprocedural ventricular perforation and eight late myocardial infarctions during follow-up. At baseline, median exercise duration was 379 s (range 60–989). At 12 months, the median change in exercise duration was 54·5 s (−526 to 501; n=60). Angina decreased by two or more classes in 26 patients.

Of 305 patients who gave informed consent for the randomised trial, 221 met all entry criteria (table 1, figure 1). The major reasons for exclusion were no ischaemia on stress testing (29 patients); voluntary decision by patient (13); patient deemed eligible for CABG or PTCA (11); no angina on exercise-tolerance testing (six). Qualifying patients were randomly assigned PTMR plus continued medical treatment (110) or continued medical treatment only (111).

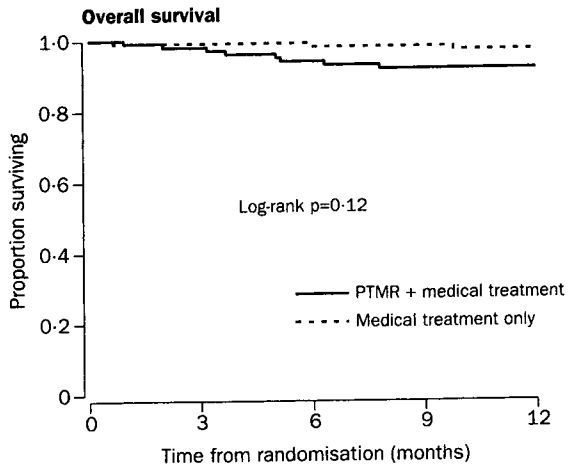
Distributions of age, sex, and results of baseline testing were similar in the two groups, but there were higher proportions of patients with hyperlipidaemia, family history of coronary-artery disease, and previous cardiac interventions in the medically treated group (table 1). However, patients in that group had a higher median score on the Seattle angina questionnaire. There was a predominance of men in both groups. Most patients had previously had myocardial infarction and CABG or PTCA. Ventricular function (as assessed at the sites) was well preserved (median ejection fraction 50%), but baseline exercise tolerance was poor (median total exercise duration 401 s).

The rates of use of individual cardiovascular medications were similar in the two groups. 52% of patients were taking β-blockers, nitrates, and calcium-channel blockers; 20% were taking β-blockers and nitrates; 15% were taking nitrates and calcium-channel blockers; and 13% were taking other combinations. 87% used aspirin daily at baseline, and 72% used lipid-lowering agents. Detailed analysis showed no significant change in the overall pattern of medication use during the course of the study in either group (data not shown).

All patients assigned PTMR underwent the procedure. The median number of channels delivered was 15 (range eight to 35). Acute complications (occurring within 24 h) included three episodes of bradycardia (one resulting in complete heart block necessitating a permanent pacemaker), one episode of ventricular tachycardia (necessitating cardioconversion), three cases of myocardial perforation (two of the free wall and one of the septum, one necessitating pericardiocentesis), one pericardial effusion, two cerebrovascular accidents (for which symptoms eventually resolved), one transient ischaemic attack, one femoral pseudoaneurysm, and one case of ischaemia of the right leg.

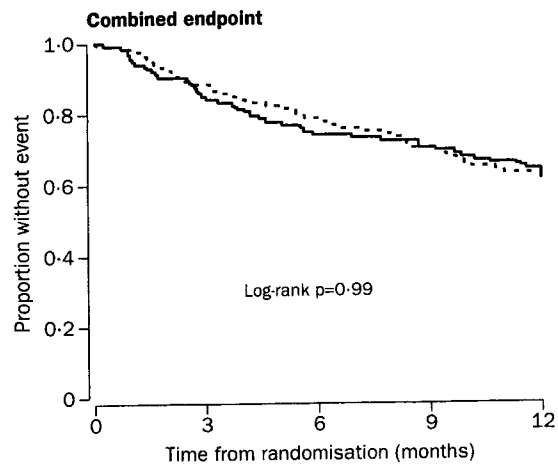
Peak creatine phosphokinase activity (available from 213 patients) averaged 145 IU/L, and the median value was 134 IU/L. The activity of the MB isoenzyme (available from 195 patients) averaged 15·8 IU/L, and the median value was 8·9 IU/L.

24 participants had PTCA, CABG, or TMR within the 1-year follow-up (figure 1). These procedures were prescribed by the patients' primary physicians (not study investigators) because of continued uncontrollable symptoms. The age and baseline characteristics of these



Number at risk

PTMR	110	107	105	98	92
Medical	111	108	106	103	99



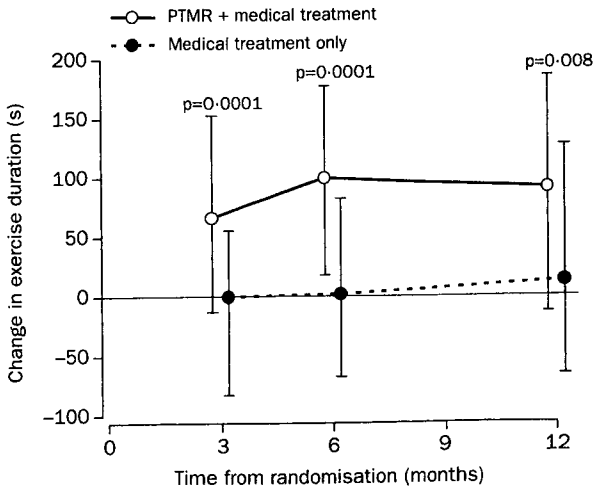
Number at risk

PTMR	110	93	81	68	57
Medical	111	87	68	63	57

Figure 2: **Kaplan-Meier curves for overall survival and a combined endpoint of death, myocardial infarction, and hospital admission (including for unstable angina)**

patients were similar to those of the overall population. These patients were followed up for 1 year after randomisation. Two died (one in each group) and one withdrew. 12 months after randomisation, there was little change in angina, but scores on the Seattle angina questionnaire had increased slightly and there were median improvements in exercise tolerance in the subgroups assigned PTMR and medical treatment only of 67 s and 48 s.

In the whole study population, there were 11 deaths during follow-up, (eight PTMR group, three medical treatment group; p=0·21, Fisher's exact test). All deaths in the medical treatment group (including one patient with reintervention) were attributed to myocardial infarction. Deaths in the PTMR group were attributed to myocardial infarction (three), cardiac arrest (three), heart failure (one), and respiratory arrest (one, a patient with reintervention). Overall survival showed no significant difference between the groups (figure 2; p=0·12, log-rank test).



Number of patients tested

PTMR	100	91	85
Medical	97	100	90

Figure 3: **Changes in total exercise duration**
Values are medians, and error bars indicate IQR.

19 patients withdrew from the study. Although complete follow-up testing was not available, all were alive at 12 months. Thus, 191 patients (92 PTMR, 99 medical care only) completed the study (figure 1).

There was an improvement in the primary endpoint, change in exercise duration from baseline to 12 months (calculated as exercise duration at 12 months minus that at baseline), in the group assigned PTMR with a median increase of 89·0 s (IQR −15 to 183; median 14·4% increase) compared with an increase of 12·5 s (−67 to 125; median 5·5% increase) in the group assigned medical treatment only (figure 3; p=0·008, Wilcoxon test), a difference of 76·5 s between the groups. If the patients who underwent other interventions were excluded, the respective changes were 90·5 s (−18 to 188) and 8·0 s (−81 to 123) (p=0·004), with a difference of 82·5 s. At 12 months, exercise duration had increased by more than 60 s in 46 (54%) patients assigned PTMR and 35 (39%) of those assigned medical treatment only (p=0·06, Fisher's exact test). At this time, exercise duration had decreased by 60 s or more in 14 patients assigned PTMR and 23 assigned medical treatment only.

At 12 months, the Canadian Cardiovascular Society class assigned by the investigators (who were aware of treatment assignment) had decreased by two or more classes in 42 of 92 patients assigned PTMR compared with only 11 of 99 assigned medical treatment only.

	PTMR				Medical treatment			
	Masked assessment grade:				Masked assessment grade:			
	I	II	III	IV	I	II	III	IV
Investigators' assessment								
I	12	7	3	11	4	1	4	0
II	0	14	16	12	0	5	5	2
III	0	0	4	8	1	4	16	23
IV	0	0	4	9	0	0	5	31

Data are % of patients in the randomised group (n=92 for PTMR, n=99 for medical treatment).
Bias in favour of PTMR is shown by the difference between groups in the total of percentages above the diagonal of those showing agreement minus the total below the diagonal.

Table 2: **Comparison of assessment of Canadian Cardiovascular Society angina class with (masked) and without (investigators') concealment of treatment allocation**

SAQ index	Median (IQR) change in score					
	3 months		6 months		12 months	
	PTMR	Medical	PTMR	Medical	PTMR	Medical
Physical limitation	17 (0 to 32)	0 (−8 to 8)	14 (3 to 36)	−3 (−11 to 8)	16 (0 to 33)	0 (−8 to 8)
Anginal stability	50 (25 to 50)	0 (−25 to 0)	25 (0 to 50)	9 (−25 to 25)	25 (0 to 50)	0 (−25 to 25)
Anginal frequency	20 (0 to 40)	0 (−10 to 20)	20 (0 to 40)	0 (−10 to 20)	20 (0 to 40)	0 (−10 to 20)
Treatment satisfaction	19 (6 to 31)	6 (−6 to 19)	13 (0 to 31)	0 (−6 to 16)	13 (0 to 31)	6 (−13 to 19)
Disease perception	33 (17 to 50)	0 (0 to 17)	33 (17 to 50)	8 (−8 to 17)	33 (17 to 50)	8 (−8 to 17)

Table 3: **Changes in Seattle angina questionnaire (SAQ) scores**

However, comparison of the investigators' assessments and those made without knowledge of treatment assignment (table 2) showed that the investigators assigned lower classes in a substantially larger proportion of the PTMR group than of the medical treatment group. 28% of the angina improvement detected by the investigators could be attributed to bias. Nevertheless, grades from the masked assessment of angina at 12 months were significantly lower with PTMR than with medical treatment only (p=0·002, Mantel-Haenszel test). 28 PTMR-group patients had angina of class II or lower compared with 12 of those in the medical treatment group. Results were similar if patients who underwent subsequent interventions were excluded.

At each assessment, scores in all five indices of the Seattle angina questionnaire had increased significantly more in the PTMR group than in the medical treatment group, both by intention-to-treat analysis (table 3) and after exclusion of patients who underwent reinterventions.

By core laboratory analysis, ejection fraction did not change from baseline to 3-month follow-up in either group (PTMR median 50% [IQR 8–75] to 51% [10–70]; medical treatment 50% [25–75] to 50% [22–70]; p=0·98).

Major adverse events occurring during follow-up are summarised in table 4. There were more episodes of angina necessitating hospital admission in the medical treatment group than the PTMR group, and higher rates of heart failure, bradycardia, and bundle branch block in the PTMR group. Other events (not shown) occurred with low frequency in both groups. Although the total number of events was lower in the PTMR group than in the medical treatment group, the time to first major cardiac event (death, myocardial infarction, or hospital admission including unstable angina) did not differ significantly between the groups (figure 2).

Discussion

Many patients have severe angina despite maximum medical therapy and percutaneous or surgical revascularisation.[11] Diffuse coronary disease, small vessels, and chronic total occlusions thwart attempts at conventional coronary revascularisation. Mirhoseini and colleagues postulated that, in severe epicardial coronary disease, creation of transmyocardial channels reaching the left-ventricular cavity might allow oxygenated blood to reach the myocardium directly, as occurs in reptile heart.[12] Although subsequent research showed that TMR does not mimic reptilian physiology,[13–15] results of clinical studies suggested that surgical TMR (with carbon dioxide and holmium:YAG lasers) improved quality of life in patients with otherwise untreatable disease,[3–5] one previous single-centre study did not corroborate these findings.[2]

Because holmium:YAG laser energy can be passed through flexible optical fibres, percutaneous systems have been developed. Studies in animals showed that this approach could be used to create a matrix of roughly equally spaced channels of depth 4–6 mm in the desired region of the ventricle.[9] A feasibility study in human beings confirmed that the device performed as intended and was safe, and provided preliminary evidence that, as with surgical TMR, PTMR reduced angina symptoms.[16,17]

The PACIFIC study has confirmed that interventional cardiologists can easily learn PTMR and that the intervention is associated with a low frequency of periprocedural complications, even during the training phase. Compared with a well-matched group of patients receiving only continued medical therapy, patients treated with PTMR and continued medical therapy had improved exercise tolerance, less severe angina (even after accounting for investigator bias), and improved perception of quality of life.

Although the difference was not significant, there were more deaths in the PTMR group than in the medical treatment group. However, mortality in the latter group was unexpectedly low. 1-year mortality after PTMR (7·3%) was similar to that after surgical TMR in the ATLANTIC study (5·4%)[3] and slightly less than that in other surgical studies of TMR.[2,4,5] In contrast, mortality was only 2·7% in the control group of the PACIFIC study, which was less than the 10% mortality in the control groups of the previous surgical studies. However, direct comparison of mortality rates between studies is precluded by the differences in populations of patients. For example, the ATLANTIC study excluded patients with severe unprotected three-vessel disease because a previous retrospective study had suggested that such patients may have 1-year mortality from surgical TMR in excess of 20%.[18] The PACIFIC study had no such restriction. In addition to mortality, there were 13 acute adverse events (12%). This rate is less than observed after surgical procedures if all types of postoperative complications are included (eg, bleeding, infection, effusions).

The improvement in exercise time and reduction in angina symptoms are lower than those observed with

Event	PTMR		Medical treatment	
	Number of patients	Events	Number of patients	Events
Death	8	8	3	3
Hospital admission for angina	34	79	52	103
Heart failure*	16	18	11	13
Myocardial infarction†	11	12	7	11
Bradycardia	7	8	1	1
CVA or TIA	7	7	4	4
Vascular complications‡	6	6	0	0
Bundle-branch block	4	5	1	1
Atrial fibrillation/flutter	4	4	4	4
Myocardial perforation‡	3	3	0	0
Ventricular tachycardia	2	2	1	1
Heart block‡	1	1	0	0
Pericardial effusion‡§	1	1	0	0

CVA=cerebrovascular accident; TIA=transient ischaemic attack.
*Need for a new prescription or two-fold or greater increased diuretic dose.
†Based on clinical judgment of investigators from presentation, myocardial enzymes, and changes in electrocardiogram.
‡All occurred periprocedurally.
§Detected on predischarge electrocardiogram.

Table 4: **Adverse events during follow-up (including periprocedural events)**

surgical TMR.[19] PTMR channels are non-transmural, and transmural channels are associated with different degrees of cardiac denervation.[7,20] This feature could be a contributing factor.[8] The location of surgically placed channels is guided by direct visualisation of the diseased arteries with the goal of achieving an even distribution around the desired vascular territory and immediately surrounding, better-perfused myocardium.

Although initially thought to be ineligible for conventional revascularisation procedures, several patients in both groups underwent CABG, PTCA, or TMR because of continued angina. These procedures were prescribed by the primary physicians (not by the PACIFIC investigators) because of the patients' continued symptoms. From the outcomes, these procedures did not, on average, provide the significant reductions in angina symptoms or improvements in exercise tolerance that they generally bring about.

A limitation of this study is that the randomised treatment allocation could not be concealed from patients or investigators. Investigator bias was detected and accounted for by comparison of masked and unmasked angina assessment. We cannot, however, exclude bias in the participants.

Although there is controversy as to the mechanisms of action, and the contribution of the placebo effect cannot be quantified, the results of this study suggest that this palliative procedure provides clinical benefits in the defined population of patients.

Contributors

Stephen Oesterle and Daniel Burkhoff co-wrote the protocol and were responsible for data interpretation and analysis and writing of the paper. All investigators contributed to recruitment and care of patients, undertook procedures, and participated in meetings to refine the protocol, to review the data, and edit the paper.

Acknowledgments

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Attachment 2.

Gray TJ, Burns SM, Clarke SC, et al. Percutaneous myocardial laser revascularization in patients with refractory angina pectoris.

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Percutaneous Myocardial Laser Revascularization in Patients With Refractory Angina Pectoris

Timothy J. Gray, MRCP, Sharon M. Burns, MRCP, Sarah C. Clarke, MRCP, Sue Tait, BSc, Linda D. Sharples, PhD, Noreen Caine, BA, and Peter M. Schofield, MD

This study aimed to determine the safety and efficacy of percutaneous myocardial laser revascularization (PMLR). Seventy-three patients with stable angina pectoris (class III or IV) who were unsuitable for conventional revascularization and had evidence of reversible ischemia by thallium-201 scintigraphy, ejection fraction of ≥25%, and myocardial wall thickness ≥8 mm were randomized to optimal medical therapy alone (n = 37) or PMLR with optimal medical therapy (n = 36). Patients were followed up at 3, 6, and 12 months. The primary end point was exercise time. Secondary end points included angina scores, left ventricular ejection fraction, quality of life, changes in medical therapy, and hospitalizations. All 36 patients randomized to PMLR underwent the procedure successfully with no periprocedure deaths. One patient developed sustained ventricular tachycardia that required electrical cardioversion, and 1 patient developed cardiac tamponade that required surgical drainage. At 12 months, exercise times improved by 109 seconds in the PMLR group but decreased by 62 seconds in the control group (p <0.01). Angina scores improved by 2 classes in 36% of PMLR-treated patients at 12 months compared with 0% of the control patients (p <0.01). We conclude that PMLR is a relatively safe procedure that provides patients with symptomatic angina relief and improvement in exercise capacity and quality of life. ©2003 by Excerpta Medica, Inc.

(Am J Cardiol 2003;91:661–666)

Percutaneous myocardial laser revascularization (PMLR) has been developed by applying a holmium-YAG laser to the endomyocardial surface using fiber optic catheters in the femoral artery. Early work with animals[1] and human patients[2,3] has suggested a low incidence of periprocedure mortality and morbidity. In the United States based Potential Angina Class Improvement From Intramyocardial Channels (PACIFIC) randomized controlled trial, PMLR was compared with medical therapy alone. Two hundred twenty-one patients were randomized on a 1:1 basis at 13 centers to either PMLR with medical therapy or medical therapy alone. The recently published results of this study[4] showed a significant improvement in exercise time and angina scores in the PMLR-treated group at 12 months. Our institution was the only non-United States based center involved in the PACIFIC trial. After ethical approval was provided, 21 patients were randomized and included in this study. We then randomized another 52 patients internally, using the same trial protocol, resulting in a cohort of 73 patients. In addition to the PACIFIC trial protocol, we conducted more detailed studies of patients' health-related quality of life. This study presents the clinical results from the patients treated at our center.

METHODS

Seventy-three patients were randomized to either PMLR with optimal medical therapy or to optimal medical therapy alone. The primary end point was exercise time on treadmill exercise testing using the modified Bruce protocol.[5] Secondary end points included angina (using the Canadian Cardiovascular Society angina classification), left ventricular ejection fraction, health-related quality of life, alterations in medical therapy and hospitalizations during the first year after randomization. Patients were followed for 1 year with no crossover from the control group to the treatment group.

Patients were recruited from November 1997 to November 1999, when there was sufficient evidence from our own data and the PACIFIC trial results[6] to make policy decisions regarding the continued use of PMLR. Follow-up of patients continued until March 2000.

Patient eligibility: After referral from their local cardiologist or general practitioner for possible laser revascularization, patients who consented to entry into the trial were assessed for suitability. Figure 1 shows a summary of these 114 patients. Inclusion criteria were stable angina refractory to maximal tolerated doses of ≥2 antianginal medications; a Canadian Cardiovascular Society angina class (CCSAS) of III or IV; evidence of reversible myocardial ischemia on thallium scintigraphy; and an ejection fraction of ≥25% with target myocardial wall thickness of ≥8 mm. Angiography was performed to assess underperfused myocardial regions, and ensure that the patient was not suitable for coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA). Patients also had to demonstrate consistent exercise capacity and were asked to perform a minimum of 2 (maximum 4) exercise tests. Two consecutive tests had to be within 20% duration

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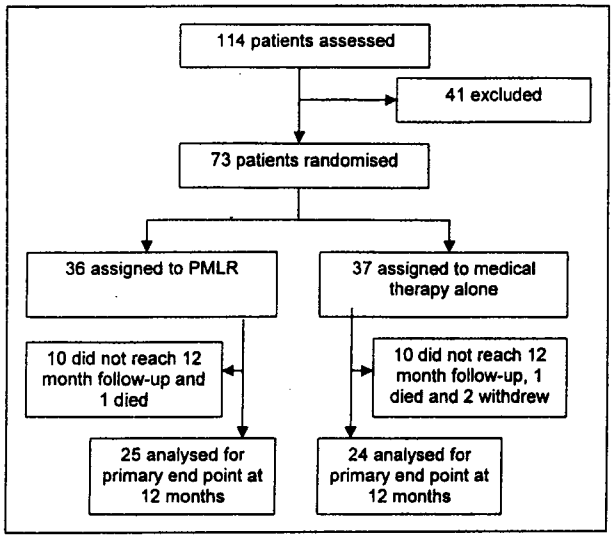

FIGURE 1. Trial profile.

TABLE 1 Causes of Exclusion from the PMLR trial

Reason for Exclusion	No.
No reversible ischemia on scintigraphy	12 (29%)
Peripheral vascular disease	3 (7%)
CCSAS <3	3 (7%)
No angina on exercise testing	2 (5%)
History of significant arrhythmia	2 (5%)
Unable to exercise	5 (12%)
Withdrew	1 (2%)
Suitable for PTCA	5 (12%)
Suitable for CABG	4 (10%)
Myocardial wall thickness <8 mm	4 (10%)

of each other and the patient had to experience typical angina on ≥1 of these tests.

Patients were excluded if they had developed a Q-wave myocardial infarction within 3 months of assessment, a non–Q-wave myocardial infarction within 6 weeks of assessment, unstable angina, or changes in cardiac medications within 2 weeks of assessment. Patients with clinically significant arrhythmias, symptomatic heart failure, severe peripheral vascular disease, aortic stenosis (aortic valve area of <1 cm^2), renal failure (serum creatinine >220 μmol/L), evidence of left ventricular thrombus, myocardial wall thickness of <8 mm in the region targeted for PMLR, or an estimated ejection fraction of <25% were also excluded.

Seventy-three patients were suitable for entry into the trial; reasons for exclusion are listed in Table 1. Suitable patients were randomized to PMLR with optimal medical therapy (n = 36) or optimal medical therapy alone (controls) (n = 37). Randomization was organized centrally. No patients from either group had subsequent PTCA or CABG, and none of the patients in the control group crossed over into the PMLR treatment group.

All patients were asked to complete a Seattle Angina Questionnaire[7] and the McGill Pain Questionnaire[8] at each visit. The Seattle Angina Questionnaire, an angina-specific questionnaire, has 5 dimensions: exertional capacity, angina stability, angina frequency, treatment satisfaction, and disease perception. Mean scores range from 0 to 100; the lower the score the worse the angina. The McGill Pain Questionnaire is a frequently used self-rating pain instrument. It requires the patient to choose up to 20 words to describe the types of pain they experience. The greater the number of words chosen (range 0 to 20), the more wide-ranging the affect on the patient. Patients are also asked to select a word that describes the intensity of the pain. Responses are ranked and a total is derived, called the "pain rating index" (range 0 to 50). Higher scores indicate more intense pain. In a second index, present overall pain intensity is measured on a scale from 0 to 5, from "no pain," through "mild" to "excruciating" pain.

PMLR procedure: The coaxial CardioGenesis PMLR (CP Pharmaceuticals, Ltd, Wrexham, Clwyd, United Kingdom) system was used. Following a bolus injection of 10,000 U of heparin to achieve an activated coagulation time of 250 to 300 seconds, the 9Fr aligning catheter was delivered into the left ventricle over a 6Fr pigtail catheter and an 0.035 J-wire. Biplanar left ventriculography and coronary angiography was performed in orthogonal views (right anterior oblique 40°, and 50° left anterior oblique with 10° cranial tilt). The diastolic outline from these ventriculograms were mapped out on acetate sheets fixed to the fluoroscopic monitors. The pigtail catheter was then replaced by the laser delivery catheter, which carried an extendible laser optical fiber. The laser fiber was capped by a 1.75-mm lens and 4 nitinol petals to retard excessive advancement of the lens into the myocardium. A gold marker facilitated radiographic positioning of the lens perpendicular to the endocardial surface. The design of the catheter system allowed manipulation in 3 different planes, allowing the operator access to all areas of the myocardium. At each potential laser site, the catheter position was checked in the 2 orthogonal views to mark the position of the laser tip and to ensure contact of the tip with the endocardial surface. The channel was then created by activating the pulsed holmium:YAG laser. Two pulse "bursts" were delivered per site (2-J pulses per burst) to create a channel 6 mm deep. Apical regions were only treated with a single burst. The position of the laser tip was marked in each view on the acetate sheets to ensure a minimum distance of 1 cm between channels. Laser revascularization continued until the target area was covered within anatomic constraints impeding catheter manipulation. At the end of the procedure, biplanar left ventriculography was repeated.

Follow-up: Serial creatinine kinase and creatinine kinase-myocardial fraction were measured every 8 hours for the first 24 hours. Transthoracic echocardiography was performed immediately after the procedure and repeated before discharge to exclude significant pericardial effusions. Patients were discharged once mobile.

Antianginal medications were continued in the groups and modifications were made according to symptoms. Patients were reviewed at 3, 6, and 12 months. At each follow-up visit, patients were interviewed, examined, and assessed by exercise test (modified Bruce pro-

TABLE 2 Baseline Patient Demographics

Characteristics	PMLR Group (n = 36)	Control Group (n = 37)	p Value
Age (yrs) (median; range)	61.5 (43–71)	61 (52–72)	0.31
Men	35 (97%)	35 (95%)	1
Diabetes mellitus	7 (19%)	11 (30%)	0.42
Hypertension	21 (58%)	18 (50%)	0.53
Hyperlipidemia	32 (89%)	30 (81%)	0.68
Previous myocardial infarction	26 (72%)	26 (70%)	0.8
Never smoked	8 (22%)	5 (14%)	1
Ex-smoker	23 (64%)	28 (76%)	1
Current smoker	5 (14%)	4 (11%)	1
Family history	26 (72%)	28 (76%)	0.79
Previous CABG	25 (69%0	21 (57%)	1
Previous PTCA	1 (3%)	2 (5%)	1
Both CABG + PTCA	9 (25%)	13 (35%)	1
Neither CABG nor PTCA	1 (3%)	1 (3%)	1
Ejection fraction (%)	48%	44%	0.1
CCSAS III	22 (64%)	26 (70%)	0.47
CCSAS IV	14 (36%)	11 (30%)	0.47
Exercise time (min) (median; range)	314 (24–624)	307 (36–683)	0.71

tocol as before), Seattle Angina Questionnaire, and McGill Pain Questionnaire. In addition, echocardiography was performed at the 3-month visit. Thallium scintigraphy was performed at each follow-up vist and these data will be reported elsewhere.

Statistical analysis: The decision to discontinue randomization in this center was based on patients demonstrating >2 minutes improvement in treadmill exercise testing and >30% of patients having a ≥2 class reduction in CCSAS in the PMLR group, compared with the control group, both of which were significant at the 1% level. These results coupled with the reported data from the PACIFIC trial were sufficient to convince the investigators of the effectiveness of PMLR in this patient group and the inappropriateness of continuing randomization.

Descriptive results of background data and procedural details are presented as mean, SD, or frequencies (percentages). For those patients with baseline and follow-up data, primary outcome results are presented as the difference in the mean change in exercise time with 95% confidence interval and compared using the Student's *t* test. For the purposes of analysis, baseline exercise was taken as the average of the 2 test results that were within 20% of each other. For secondary outcomes, the groups were compared using Fisher's exact test (2-sided) for categorical data, and the Mann-Whitney U test for ordinal measurements. Due to the decreasing numbers of patients reaching 3-, 6-, and 12-month follow-up, results were analyzed separately for each time interval and no adjustments were made for repeat dependent significance testing. Therefore, isolated significance results were treated skeptically. Measurements that showed consistently significant differences between groups and those that were $p < 0.01$ are described as significant.

RESULTS

Compliance: Patient compliance is shown in Figure 1. One hundred fourteen patients were assessed; 41 were unsuitable and 73 were randomized to 2 groups (36 to PMLR, 37 to controls). In the 12 months after assessment, there was 1 death in the PMLR group, secondary to a myocardial infarction 82 days after the PMLR procedure. In the control group, there was 1 death and 2 withdrawals from the trial. The death was due to myocardial infarction at 30 days after assessment. The 2 patients who withdrew did so voluntarily; 1 was not prepared to continue as a control patient and 1 had a peripheral arterial embolus.

Demographics: Baseline characteristics for both groups were similar and are listed in Table 2. Most patients were men, a median age of 62 years. About 2/3 had CCSAS III, most had had previous coronary revascularization and ≥1 myocardial infarction. Only 1 patient had no risk factors at all.

PMLR procedure: All patients randomized to the PMLR group underwent the procedure as scheduled. Mean time from randomization to procedure was 23 ± 25 days and 27 of 36 patients (75%) were in hospital for 2 days after the procedure. Only 1 patient remained in hospital for >4 days. There were no periprocedure deaths. Fourteen patients had the anterior wall treated, 11 the inferior wall, and 6 the lateral wall. Five patients had 2 walls treated (2 anterolateral and 3 inferolateral). Mean time to create the channels was 32 minutes with an average fluoroscopic time of 33 minutes. The peak creatinine kinase measured in the first 24 hours was an averaged of 135 ± 50 IU/L (normal range 10 to 195) with a mean creatinine kinase-myocardial fraction of 32 ± 16 IU/L (normal range 0 to 12). None of the creatinine kinase and creatinine kinase-myocardial fraction values were suggestive of myocardial infarction, and there were no electrocardiographic changes suggestive of myocardial infarction.

Complications included 1 episode of symptomatic ventricular tachycardia requiring electrical cardioversion, 1 episode of temporary heart block, and 1 myocardial wall perforation requiring a surgical pericardial window. During the procedure, one patient developed transient right bundle branch block and 5 patients developed left bundle branch block. All of these were transient, except for 1 which had resolved by the 3-month follow-up. One patient experienced a transient ischemic attack 5 days after the procedure, but had full resolution of symptoms.

Exercise times: At 3 months, the PMLR group improved their exercise tolerance by 102 ± 132 seconds, whereas the control group deteriorated by 26 ± 91 seconds (difference of 128 seconds, 95% confidence interval 71 to 185, $p < 0.01$). These improvements were sustained in the PMLR group at 6 and 12 months, whereas the control group continued to deteriorate throughout the follow-up period. At 12 months,

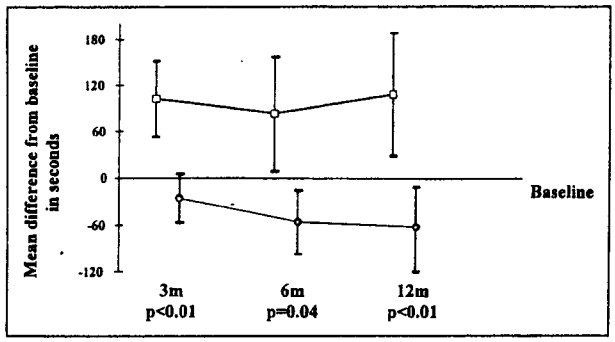

FIGURE 2. Mean difference in exercise times from baseline (in seconds). *White squares*, PMLR group; *white circles*, control group.

the PMLR group had improved their exercise tolerance by a total of 109 ± 186 seconds, whereas the control group had deteriorated by 62 ± 125 seconds (difference of 171 seconds, 95% confidence interval 78 to 265, $p < 0.01$). These findings are shown in Figure 2. The improvement from baseline in the PMLR group remained significant to 12 months (3 months, $p < 0.01$; 6 months, $p = 0.04$; 12 months, $p = 0.01$). However, this relies on multiple dependent significance testing; adjusting for multiple comparisons would result in nonsignificance at 6 months ($p > 0.05$).

Angina scores: At baseline, 22 of 36 patients in the PMLR group (61%) had CCSAS class III symptoms and 14 of 36 patients (39%) had class IV symptoms. After the PMLR procedure, angina levels continued to improve; by 12 months, 18 of 25 patients (72%) were in class I and/or II with only 7 of 25 (28%) in class III and/or IV.

In the control group, baseline symptoms were similar. There was little change at 3 and 6 months, but by 12 months, 2 of 24 patients (8%) were in class II, 10 of 24 (42%) were in class III, and 12 of 24 (50%) were in class IV.

At 3 months, a decrease of ≥2 classes was seen in 5 of 31 PMLR patients (16%) and 0 of 34 control patients (0%) ($p = 0.02$). Continued improvement was seen at 12 months in the PMLR group in 9 of 25 patients (36%), but 0 of 24 (0%) control patients showed improvement ($p < 0.01$).

Health-related quality of life: Seattle Angina Questionnaire scores are shown in Figure 3. Angina stability and frequency improved at 3 months in the PMLR group, but then decreased again at 6 and 12 months, although levels still remained above baseline. Angina frequency remained constant throughout follow-up in the control group, but with a decrease in angina stability. The PMLR group remained significantly better during the follow-up period.

The PMLR group was significantly better than baseline at 3, 6, and 12 months with regard to exertional capacity, anginal stability, anginal frequency, disease perception, and treatment satisfaction at 6 and 12 months ($p < 0.01$ in all cases). All these variables remained significant when adjusted for multiple comparisons ($p \leq 0.05$).

The McGill Pain Questionnaire showed the PMLR group significantly worse than the control group at baseline in the pain rating index ($p < 0.05$) and number of words chosen scores ($p < 0.05$). However, by 3 months the PMLR group had improved; thus, they were significantly better than the control group in all dimensions ($p < 0.01$). This was maintained to 12 months ($p < 0.05$).

Ventricular function: Baseline ejection fractions were estimated by use of acoustic quantification, and were 48% in the PMLR group and 44% in the control group ($p > 0.05$). We found that left ventricular function did not change.

Drug therapy: No significant differences were seen in the medical treatment between the 2 groups at baseline. There was no statistical difference between the 2 groups in medication dose changes or antianginal class changes. These changes are listed in Table 3.

Hospitalization: Hospitalization rates for angina, in addition to the procedure, were not significantly different (PMLR group 24 hospitalizations in 309 patient-months of follow-up; control group 22 hospitalizations in 321 patient-months of follow-up) ($p = 0.68$).

DISCUSSION

Our experience with the CardioGenesis laser system demonstrates the low mortality and morbidity associated with PMLR compared with transmyocardial laser revascularization. We show that not only is there a significant improvement in subjective angina and quality-of-life scores, objective evidence in the form of improved exercise times also confirms this clinical improvement. Although there was an overlap of 21 patients, our data show close correlation with the results from the PACIFIC study,[4] the only published randomized controlled trial comparing PMLR to medical therapy. Recently, a double-blinded, randomized, controlled trial using the same laser system showed improved angina scores, although they were unable to demonstrate significantly improved exercise times in the PMLR group.[9] Much interest was created when the Direct myocardial revascularization In Regeneration of Endomyocardial Channels Trial (DIRECT) was halted early. This study was single blinded, and used an alternative laser delivery system. All patients had electromechanical mapping of the left ventricle, but 50% had been randomized to proceed to laser revascularization during the same procedure. Patients were blinded to this treatment. Initial results failed to show any benefit in the laser-treated group. Interestingly, during a nonblinded run-in phase, a significant improvement in symptoms was seen in the treatment arm. We believe that this result may be partially due to the different delivery method and laser characteristics of this alternative system, and would caution comparison with the CardioGenesis system; however, we believe that the effects of placebo should not be underestimated. The most significant limitation of this study is likely to be patient and investigator bias due to the unblinded trial design.

Compared with TMLR, an important contraindication to PMLR is severe peripheral vascular disease

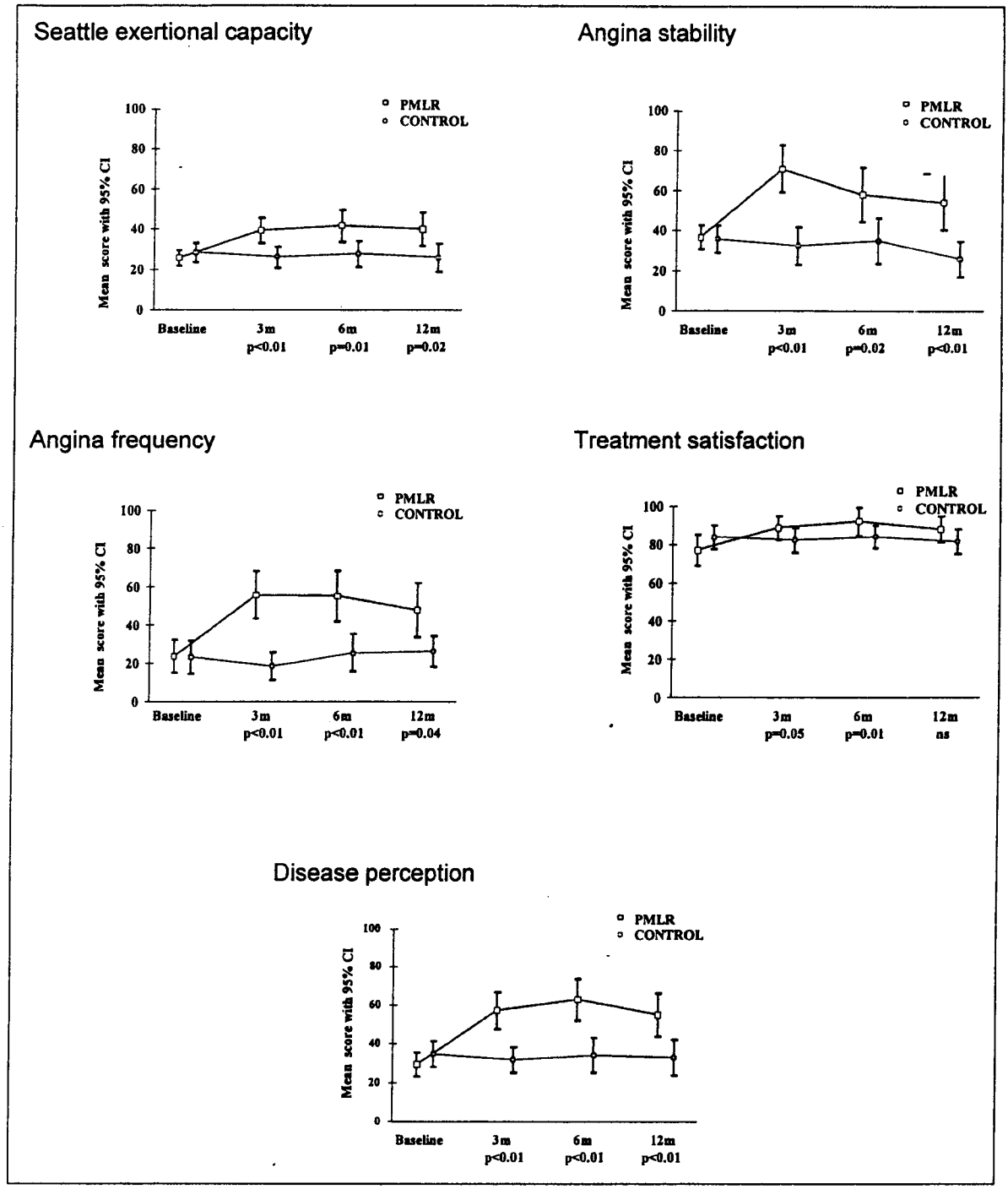

FIGURE 3. Seattle Quality of Life scores. CI = confidence intervals.

precluding femoral access with the 9Fr laser guide catheter. Three patients were assessed for the trial and excluded for this reason.

The deterioration in the exercise times of the control group was not expected in the light of past experience with TMLR. These patients had similar distributions of class III and IV symptoms when compared with the control group of our TMLR trial. The only major difference in demographics was the higher incidence of diabetes in the control group of the PMLR trial, which may help to explain the apparent accelerated deterioration in this group. These exercise times corresponded with a gradual deterioration in angina score throughout the 1-year follow-up period.

Although placebo is likely to play a significant role in the results seen from our data, we believe that the significant sustained differences in the PMLR arm goes against placebo effect as the only mechanism. Early studies using positron emission tomography have shown improved perfusion in the laser-treated

TABLE 3 Number of Changes to Cardiac Medications During the Follow-up Period for Each Group

	Class Addition	Dose Increase	Class Removal	Dose Reduction
Antianginal medications				
PMLR	7	19	7	8
Control	7	11	3	4
Heart failure medications				
PMLR	2	2	1	0
Control	2	3	1	0
Other cardiac medications				
PMLR	1	5	0	0
Control	4	2	1	0

Medication classes include β blockers, calcium antagonists, potassium channel blockers, nitrates, and opiates for antianginal drugs; angiotension-converting enzyme inhibitors and diuretics for heart failure medications, and antiplatelet drugs and lipid-lowering therapy for other cardiac medications.

areas compared with nontreated myocardium in small numbers of patients.[14] Other possible mechanisms of action for PMLR include angiogenesis in the ischemic myocardium[15–20] and cardiac denervation.[21–24] Most groups now accept that the channels do not remain patent for long,[25–29] and therefore, improved perfusion is unlikely to be as a direct result of channel creation.[30]

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Attachment 3.

Salem M, Rotevatn S, Stavnes S, et al. Usefulness and Safety of Percutaneous Myocardial Laser Revascularization for Refractory Angina Pectoris.

Am J Cardiol 2004;93:1086-91.

Usefulness and Safety of Percutaneous Myocardial Laser Revascularization for Refractory Angina Pectoris

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This prospective, double-blind, randomized, sham-controlled trial was designed to control for patient and investigator bias in assessing symptomatic improvement after percutaneous myocardial laser revascularization (PMLR) therapy. Eighty-two patients with stable angina pectoris (class III or IV) not amenable to conventional revascularization and with evidence of reversible ischemia, ejection fraction ≥25%, and myocardial wall thickness ≥8 mm were randomized to either PMLR with optimal medical therapy (n = 40) or to a sham procedure with optimal medical therapy (n = 42). With the exception of 1 laser technician, all patients, investigators, and assessors were blinded to treatment through the 12-month follow-up. The primary end point was restricted to Canadian Cardiovascular Society angina class improvement to limit the number of patients exposed to a sham procedure. Secondary assessments included medication usage, quality of life, exercise testing, ejection fraction, and hospitalizations. The incidence of serious adverse events, as determined by cardiac event-free survival at 12 months, was similar between groups. At 12 months, Canadian Cardiovascular Society angina scores improved by ≥2 classes in significantly more PMLR-treated patients than sham control patients (35% vs 14%, p = 0.04). Angina-specific quality-of-life measures were significantly higher in the PMLR group at each follow-up (p <0.05). Exercise and medication usage was similar between groups at 12 months. We conclude that PMLR therapy is reasonably safe and effective as symptomatic improvement in patients refractory to medical therapy, and that the clinical benefit is not attributable to placebo effect or investigator bias. **©2004 by Excerpta Medica, Inc.**

(Am J Cardiol 2004;93:1086–1091)

In 1995, the Norwegian Ministry of Health prohibited surgical laser revascularization as a routine clinical option because of concerns regarding procedural morbidity and mortality. This decision was revisited in 1999 through an extensive, independent-panel published review.[1] Although the ban was withdrawn, the lack of evidence discounting a placebo effect as the primary mechanism of the observed symptomatic improvement has limited the routine clinical use of the technology. To address the panel's finding, and because a sham surgical laser revascularization trial was not ethically possible, we designed a double-blinded clinical trial (the Blinded Evaluation of Laser Intervention Electively For angina pectoris [BELIEF]) to control for patient bias (the placebo effect) and investigator bias in determining the symptomatic benefit of percutaneous myocardial laser revascularization (PMLR) treatment using the same device system for which initial unblinded trial results were reported.[2]

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METHODS

Participants: After referral for possible laser revascularization, consenting patients were assessed for suitability at the 2 participating institutions (Haukeland Hospital, Bergen, Norway, and Ulleval University Hospital, Oslo, Norway). The following criteria were necessary for inclusion in the study: stable Canadian Cardiovascular Society (CCS) class III or IV angina refractory to maximally tolerated doses of ≥2 antianginal medications; evidence of reversible myocardial ischemia on exercise testing or technetium sestamibi stress myocardial perfusion scanning; and ejection fraction ≥25% and wall thickness ≥8 mm in the target region for PMLR by echocardiography. Angiography was performed to ensure that patients were not suitable for conventional revascularization methods (coronary artery bypass grafting or percutaneous coronary intervention). Exclusion criteria included: recent myocardial infarction; symptomatic heart failure with exercise limited by dyspnea; significant ventricular arrhythmias requiring long-term therapy; ventricular thrombus, significant peripheral vascular disease, aortic valve stenosis, or a mechanical aortic prosthesis; and unstable angina requiring hospitalization within 14 days before consent or necessitating a significant change in medication.

The ethics committees approved the trial, and all patients signed informed consent after the investigative nature of the trial and its risks and merits had been fully explained. The primary end point was improvement in CCS angina class as determined by a blinded

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independent assessor. Secondary assessments included medication usage, quality of life using the Seattle Angina Questionnaire,[3] chronotropic exercise assessment using a limited protocol,[4] left ventricular ejection fraction, and hospitalizations. Randomization of 82 patients occurred centrally between March 1999 and June 2000 to PMLR plus optimal medical therapy or to a sham procedure plus optimal medical therapy, with 12-month follow-up continuing through June 2001. No patient underwent a subsequent revascularization procedure.

Sample size and statistical analysis: The sample size calculation reflects a balance between the need to limit patient exposure to potential hazards resulting from a sham procedure while producing the opportunity for a statistically and clinically justifiable result. As such, the trial was designed to detect a clinically relevant difference in the proportion of patients with ≥1 class reduction in CCS angina score, assuming 20% improvement in the sham group. Using a 2-sided significance level (α) of 0.05 and 80% power, 39 patients in each group were calculated to be necessary based on the uncorrected chi-square statistic for analysis. To account for possible dropouts, the total trial enrollment was 82 patients. The trial was not powered for secondary assessments.

Results are provided as mean ± SD for continuous variables and as a proportion (percentage) for categorical variables. The 2-sided, 2-sample Student's *t* test was used for analysis of continuous data compatible with a normal distribution. The exact Mann-Whitney U statistic test and Fisher's exact test were used for CCS angina class improvement analyses; missing values are imputed to worst case. For adverse event data, patients with events were compared with the log-rank test. A p value (2-sided) ≤0.05 was considered statistically significant. To avoid confounding variables, baseline evaluations were performed and documented before randomization. Patients received no compensation for participation.

Randomization, blinding, and interventional procedure: The independent data management center provided each investigational site in advance with a set of sealed and coded randomization envelopes, which were maintained in a locked cabinet accessible only by the laser technician. Patients were randomly assigned (1:1) to PMLR or sham treatment; all patients continued their established prerandomization medical therapy.

To assure blinding of the patients, investigators, and staff, the laser console and the laser technician were placed behind an opaque curtain out of view in the catheterization laboratory. An activated coagulation time of ≥250 seconds was targeted in all patients, followed by instrumentation with the coaxial CardioGenesis PMLR system (CardioGenesis Corporation, Foothill Ranch, California). The 9Fr-aligning catheter was placed over a pigtail catheter and J-wire into the left ventricle. The pigtail catheter was then replaced by the laser catheter, which contains an optical fiber terminated with a focusing lens (1.6-mm spot size) and nitinol depth-retarding petals at the distal end.

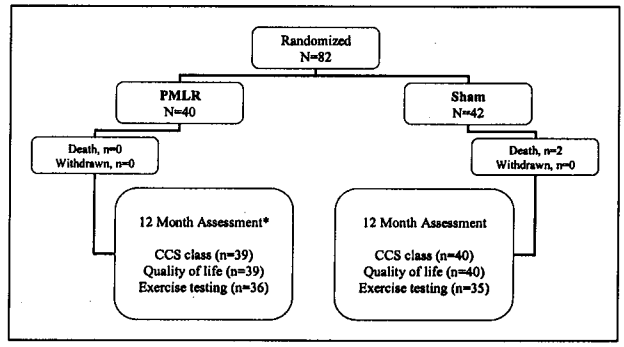

FIGURE 1. Patient accountability flow diagram. *One PMLR patient who had a cerebrovascular accident 3 months after the procedure could not attend subsequent effectiveness assessments.

Laser catheters[2] were calibrated before the procedure to produce an identical response from the laser: 1 catheter was placed in the left ventricle of the patient; the other catheter was placed in a lead box. At the time the laser technician opened the treatment assignment envelope, the catheter located in the left ventricle (PMLR) or in the lead box (sham) was connected to the laser console by the technician. At each targeted channel site, the location of the catheter tip was checked using biplane fluoroscopy in 2 orthogonal views to ensure contact with the endocardium. The investigator then activated the foot switch to create channels using 2 "bursts" (each consisting of two 2-J pulses) of laser energy. Each channel was tracked fluoroscopically using markings on fixed acetate sheets. For the sham group, the laser catheter was connected to a hidden lead box and, as such, no laser channels were actually formed in the myocardium. There was no visual or audible feedback from the laser system that could reveal the randomized assignment. Before completion of the 12-month assessments, the laser technician was the only unblinded person involved in the trial.

Immediately after the procedure and before discharge, an echocardiogram was recorded to exclude the occurrence of significant pericardial effusion and to assess wall motion, and blood samples were drawn for cardiac enzyme analyses. Blood samples were frozen and not analyzed until after completion of the trial to ensure blinding. Patients were also assessed after the procedure with serial electrocardiograms to rule out serious cardiac adverse events.

RESULTS

Patient characteristics: Patient follow-up is shown in Figure 1; 82 patients were randomized (PMLR n = 40, sham n = 42). All baseline characteristics (Table 1) were similar between groups.

Procedural outcomes: In each group, comparable channel placements were made (PMLR 19 ± 4.5 vs sham 20 ± 3.6; p = 0.30) over comparable procedure durations (PMLR 36 ± 16 minutes vs sham 37 ± 12 minutes; p = 0.66). The primary target region within the left ventricle was the lateral wall (n = 67; 82%), followed by the inferior (n = 51; 62%) and anterior (n

TABLE 1 Baseline Patient Characteristics

	PMLR (n = 40)	Sham (n = 42)	p Value
Age (yrs)	65 ± 9.3	67 ± 9.8	0.44
Men	38 (95%)	37 (88%)	0.43
Site: Haukeland/Ullevaal	28 (70%)/12 (30%)	29 (69%)/13 (31%)	1.00
Congestive heart failure	1 (2.5%)	1 (2.4%)	1.00
Diabetes mellitus	5 (13%)	8 (19%)	0.61
Family history of coronary artery disease	28 (70%)	31 (74%)	0.81
Prior bypass grafting only	14 (35%)	14 (33%)	0.86
Prior PCI only	2 (5.0%)	4 (9.5%)	
Prior bypass grafting or PCI	36 (90%)	37 (88%)	
Prior myocardial infarction	25 (66%)	29 (69%)	0.86
Smoker	29 (73%)	32 (76%)	0.63
Systemic hypertension	19 (48%)	20 (48%)	1.00
Ejection fraction (%)	64 ± 12	63 ± 12	0.65
Serum cholesterol (mmol/L)	6.7 ± 1.9	7.0 ± 2.1	0.47
CCS class III/IV	36 (90%)/4 (10%)	35 (83%)/7 (17%)	0.52
Exercise time (s)	610 ± 222	585 ± 235	0.64
Medications			
ACE inhibitors	8 (20%)	11 (26%)	0.60
Aspirin	35 (88%)	33 (78%)	0.38
β blockers	35 (88%)	38 (90%)	0.73
Calcium antagonists	20 (50%)	25 (59%)	0.26
Diuretics	4 (10%)	9 (19%)	0.35
Lipid-lowering agents	34 (85%)	40 (95%)	0.15
Nitrates	37 (93%)	37 (88%)	0.71

Values are expressed as mean ± SD or numbers (%).
ACE = angiotensin-converting enzyme; PCI = percutaneous coronary intervention.

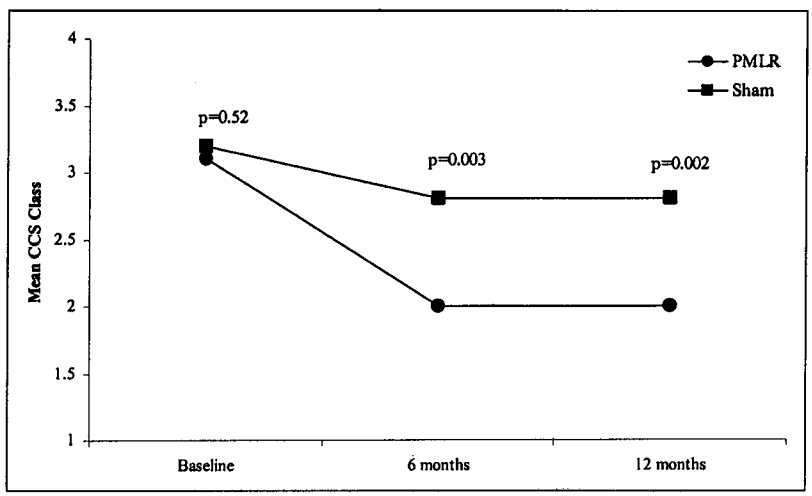

FIGURE 2. Mean CCS angina class assessment results.

= 31; 38%) walls, with most patients (65%) treated in 2 regions. Periprocedurally, there were no PMLR deaths and 1 sham death attributed to acute myocardial infarction. Autopsy showed no evidence of perforation, tamponade, or device relatedness. None of the 24-hour peak creatine kinase or creatine kinase–myocardial fraction values determined after trial completion were indicative of myocardial infarction; however, the mean PMLR values were significantly higher than the mean sham values ($p < 0.05$) due to the laser treatment (creatine kinase, 211 ± 119 vs 159 ± 82 IU/L; creatine kinase–myocardial fraction 28 ± 60 vs 12 ± 7 μg/L). Predischarge electrocardiograms showed no evidence of myocardial infarction. Complications in the PMLR group included myocardial perforation with pericardiocentesis, arrhythmia treated medically, and nonspecific chest pain; complication in the sham group were pericardial effusion and transient ischemic attack.

CCS class: All patients were in CCS class III or IV at baseline, with distributions comparable between groups (class III/IV: 90%/10%, PMLR vs 83%/17%, sham; $p = 0.52$). All patients except for 1 PMLR patient (cerebrovascular accident) and 2 sham patients (death) were available for 6- and 12-month follow-up: 79 of 82 randomized patients (96%) had blinded CCS assessments at 6 and 12 months. Mean results are shown in Figure 2. At 6 months, significantly more PMLR than sham patients improved by ≥1 CCS class (63% vs 36%, $p = 0.03$) or by ≥2 CCS classes (40% vs 12%, $p < 0.01$) from baseline. This significant improvement was sustained at 12 months in terms of ≥1 CCS class improvement (63% vs 38%, $p = 0.04$) and ≥2 CCS class improvements (35% vs 14%, $p = 0.04$) from baseline. In a multivariate analysis of baseline predictors of ≥2 CCS angina class improvements, treatment assignment and baseline CCS class IV were the only significant independent predictors. The estimated odds ratio of ≥2 CCS class improvement at 1 year after adjustment for baseline CCS class is 3.8 (95% confidence interval 1.2 to 12).

Medication usage: There were no significant between-group differences in medical therapy usage at baseline. As per trial design, medical therapy remained stable in both groups at 12 months, with no significant dose changes in any medication including nitrates (Table 2).

Quality of life: The Seattle angina questionnaire was designed specifically to assess functional status and health-related quality of life in patients with angina, and has 5 components each assessed on a 100-point scale. Scores were comparable among groups at baseline and improved in both groups during follow-up (Figure 3). At 6 and 12 months, scores for the angina-specific components—angina stability and frequency—were significantly higher ($p < 0.05$) in the PMLR group than in the sham group.

Exercise: The chronotropic assessment exercise protocol was designed for use in functionally limited patients with an implanted pacemaker involving a warm-up, modest work increments, and slowly in-

TABLE 2 Medication Usage at Follow-up

	12-month Usage			No. of Dose Changes at 12 Months			
				Decreased		Increased	
	PMLR	Sham	p Value	PMLR	Sham	PMLR	Sham
Aspirin	32 (89%)	30 (81%)	0.52	1	0	1	1
ACE inhibitors	7 (19%)	12 (32%)	0.29	0	0	0	0
β blockers	30 (83%)	33 (89%)	0.52	6	1	1	2
Calcium channel blockers	18 (50%)	23 (62%)	0.35	5	1	1	1
Diuretics	4 (11%)	5 (14%)	1.00	0	0	0	0
Lipid-lowering agents	32 (89%)	24 (92%)	0.71	0	0	0	0
Nitrates	33 (91%)	34 (92%)	1.00	3	3	1	6

Abbreviation as in Table 1.

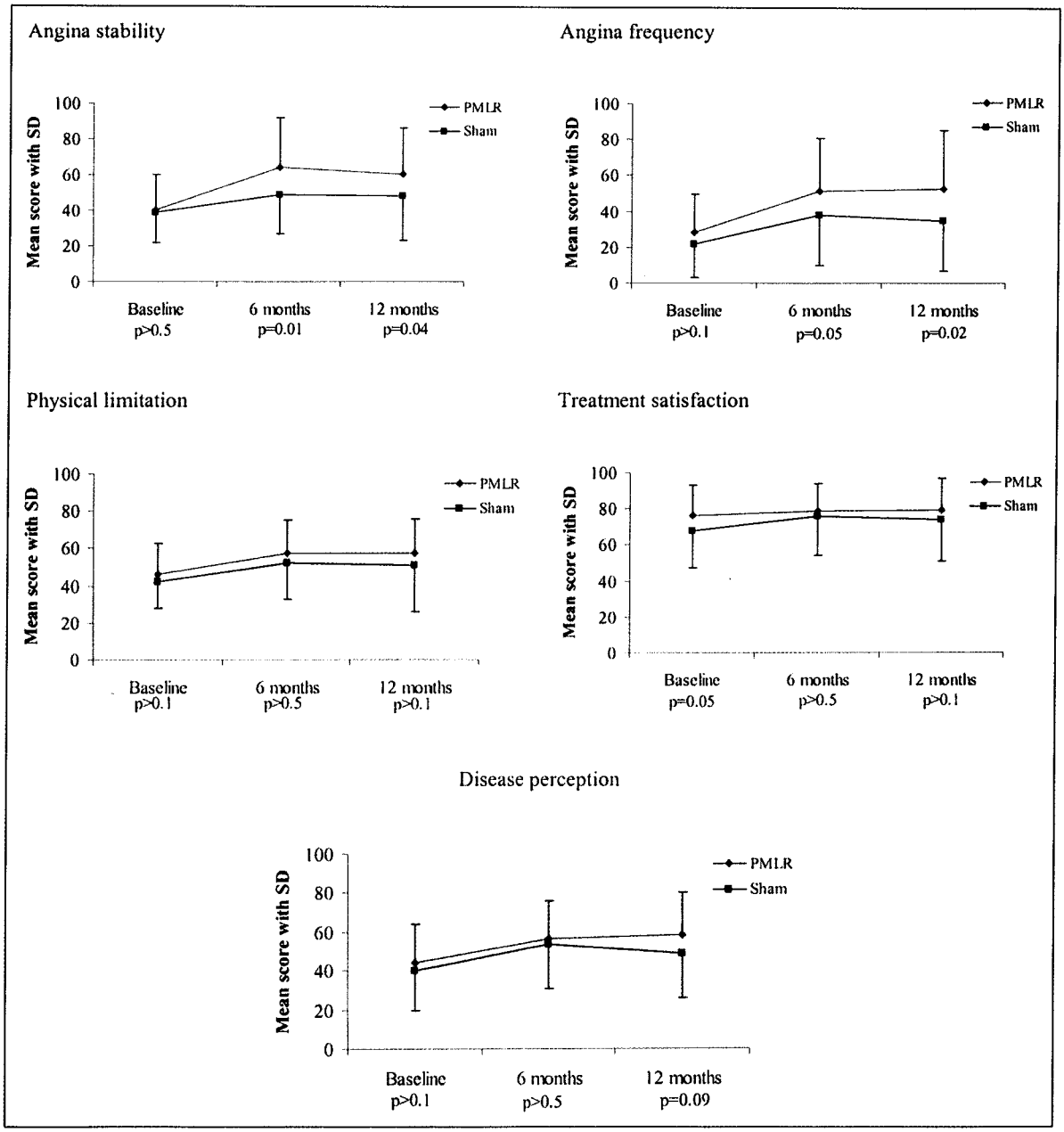

FIGURE 3. Seattle Angina Questionnaire quality-of-life scores. Higher scores indicate higher quality of life.

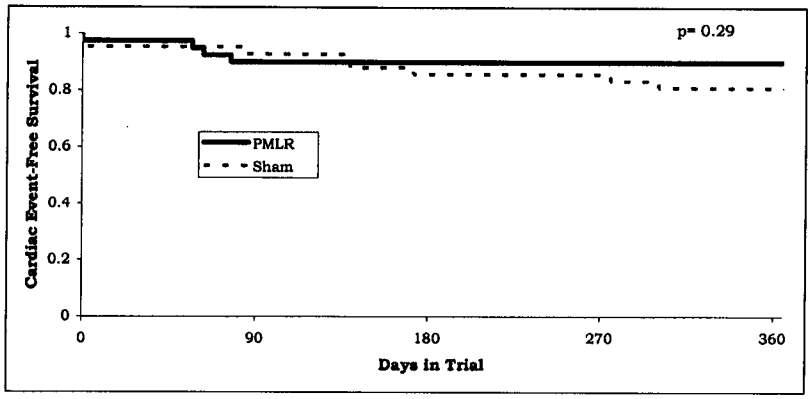

FIGURE 4. Kaplan-Meier cardiac event-free survival (freedom from death, myocardial infarction, cerebrovascular accident/transient ischemic attack, myocardial perforation, and rehospitalization) through 12 months (p = 0.29, log-rank test).

creasing speed and grade. Exercise times were comparable between groups at baseline (PMLR 610 ± 222 seconds vs sham 585 ± 235 seconds; p >0.5). Exercise testing during follow-up was performed in approximately 1/3 of patients using bicycle and treadmill, and in 2/3 of patients using treadmill alone. Results showed no significant between-group differences at 12 months in total time (PMLR 620 ± 245 seconds vs sham 604 ± 229 seconds; p >0.1). Oxygen uptake and respiratory exchange ratio did not change significantly during follow-up in either group.

Ejection fraction: Baseline ejection fractions were comparable between groups (PMLR 64%, sham 63%; p = 0.65) and did not change during follow-up.

Adverse events and hospitalizations: One additional sham patient died during follow-up (month 3) due to a suspected myocardial infarction. All-cause mortality at 1 year was similar between groups (PMLR 0%, sham 5%; p = 0.17 [log-rank test]). Hospitalizations during follow-up included: PMLR group: cerebrovascular accident, claudication, lower leg edema, 2 peripheral vascular interventions, and 3 angina hospitalizations; sham group: myocardial infarction, transient ischemic attack, atrial fibrillation, dyspnea, peripheral vascular intervention, leg edema/pain, and 3 angina hospitalizations. The cardiac event-free survival was similar between groups at 1 year (p = 0.29, log-rank test [Figure 4]).

DISCUSSION

Surgical laser revascularization was developed for the treatment of patients unsuitable for conventional therapies due to diffuse disease[5] and has been evaluated in 5 prospective, randomized trials against optimal medical therapy.[6–10] Results at 1 year show superior angina relief and improved event-free survival/quality of life, yet with equivocal results in perfusion improvement. PMLR was developed as a less invasive alternative[11] to avoid general anesthesia/thoracotomy with the associated risks, and to reduce recuperation time. In 3 prospective, randomized trials, PMLR using ≥1 mm of multipulsed fiber optic devices provided superior angina relief and improved exercise tolerance/quality of life compared with optimal medical therapy.[2,12,13] In another study involving a different (bypass-eligible) patient group with chronic total occlusions, no significant benefit was observed[14]; however, incomplete follow-up (50% through 6 months) greatly reduces the meaning of these results.[15] Despite these overall favorable clinical benefits, the mechanism(s) of action remain unclear. Several potential mechanisms, including angiogenesis and denervation, continue to be the subject of ongoing investigations.[16–20] The placebo effect[21] has also been discussed as a potential factor because none of the completed trials included a blinded control group.

Compared with surgical treatment, our findings and those of other investigators[2,12,13] using the CardioGenesis PMLR device, demonstrate the low mortality and substantially reduced morbidity associated with this device. The procedural complication and 1-year mortality rates were lower than rates observed in surgical laser revascularization trials.[6–10] We have shown in this randomized, double-blind, sham-controlled trial of PMLR in "no option" patients, that laser therapy is superior to sham intervention for reducing CCS angina class by ≥2 classes; this study also confirms the significant 1-year results reported in the unblinded trials using this same device (46% vs 11%, PMLR vs control; p <0.001 and 36% vs 0%, PMLR vs control; p <0.01).[2,12] The improvement we observed in the placebo group (12% and 14% at 6 and 12 months, respectively) accounts for patient and investigator bias in CCS angina class improvement owing to the rigorous blinding of patients, investigators, and independent assessors to 1 year.

Although these findings reflect those of the unblinded trials that used the identical PMLR system, they are contrary to the negative findings of the single-blinded Direct myocardial revascularization In Regeneration of Endomyocardial Channels trial, which used different laser parameters, methods, and delivery system.[22] All patients underwent a diagnostic electromechanical left ventricular mapping intervention during this study, and 2/3 were randomized to continue to 1 of 2 laser treatment regimens during the same procedure. Results showed no gradient of benefit in the laser-treated groups. Because the laser characteristics of the system used are substantially different from those of the system used in our study (e.g., no endocardial puncture or channel ablation, 1 pulse, 80% smaller laser spot size), the respective study results should be considered independently.

Consistent with significant CCS class improvement, the Seattle Angina Questionnaire angina-related subscales were significantly increased at 6 and 12 months. Other components were not significantly dif-

ferent between groups, possibly due to the less specific nature of these components, the trial size, or to the trial design. A significant change in exercise duration was not observed in our trial, also possibly owing to the limited trial size, the use of a mild exercise protocol without a baseline reproduciblity element, and the use of treadmill and bicycle testing in the follow-up of some patients. Moreover, the large SDs in baseline times would have required a fivefold larger sample size to detect a 10% change from baseline; the exposure of such a large population to a sham procedure was not deemed ethical. Myers et al[20] reported the blinded core laboratory analysis results of larger randomized, unblinded trials with this same PMLR device[2] and the surgical device[10] using the modified Bruce treadmill protocol for 1 year. Requiring baseline reproducibility, they found significant improvements at 1 year, and concluded that the devices improved functional capacity and relieved pain without substantial denervation or silent ischemia. Other randomized surgical trials do not show significant changes in exercise time; however, they demonstrated increased time to chest pain[8,9] and reduced nitroglycerin use[8] in treated patients at 12 months. Thus, our trial design does not address the potential role of patient bias in these previous exercise results.

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