Technology Assessment

Technology Assessment Program

Percutaneous Myocardial Laser Revascularization and Transmyocardial Laser Revascularization

Agency for Healthcare Research and Quality
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1. INTRODUCTION

1.1 Overview

Over the last two decades, transmyocardial laser revascularization (TMR) and percutaneous myocardial laser revascularization (PMR) have been developed to treat refractory angina in patients with coronary artery disease that is not amenable to revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). These new techniques create multiple, small channels in ischemic myocardium using laser irradiation with the goal of improving local blood flow.

1.2 Request by Centers for Medicare and Medicaid Services

The Agency for Healthcare Research and Quality (AHRQ), on behalf of the Centers for Medicare and Medicaid Services (CMS), has requested a technology assessment on TMR and PMR in preparation for a Medicare Coverage Advisory Committee meeting on this topic.

The specific aims of this technology assessment are as follows:

1. Provide a summary and description of the technology.
2. Review the peer-reviewed clinical literature on the outcomes associated with the use of:

a. TMR as a stand-alone procedure;

b. TMR used together with CABG;

c. PMR.

3. Review of available information on clinical trials underway as a horizon scan for this technology.

In addition, studies on the mechanism of action and the specific lasers used for each of the procedures were reviewed, and a description of those findings is included in this report.

1.3 Organization of the Report

A background section provides an overview of how the technologies work, what lasers are used, and the status of the technologies in terms of Food and Drug Administration (FDA) approval and CMS coverage. In addition, several common hypotheses on the mechanism of action for laser revascularization are summarized.

Results are discussed under two main headings: efficacy and safety/utilization. To assess the efficacy of TMR and PMR, we reviewed randomized controlled trials (RCTs). For the more general questions of

safety and utilization – phenomena that may not be well reflected in a trial setting – we focused on observational studies. Under each of the main headings, we provide an overview of all the studies in that section, followed by brief summaries of each study.

2. BACKGROUND

2.1 Background and Rationale for Use of the Technologies

Sen and colleagues first described transmyocardial revascularization using hollow needles in 1965 [Sen, 1965]. This technique attempted to mimic reptilian hearts, which are predominantly perfused by endothelium-lined channels that fill directly from the ventricular cavity [Allen, 1999; Huikeshoven, 2002]. Since Sen's pioneering work, investigators have examined other methods for channel creation including drills, ultrasound, cryotherapy, radiofrequency, and saline jets [Huikeshoven, 2002]. These experiments eventually resulted in Mirhoseini and colleagues' 1981 report of transmyocardial revascularization using laser irradiation [Mirhoseini, 1981]. Because the carbonization associated with its use was observed to inhibit lymphocyte, macrophage, and fibroblast migration, laser revascularization was felt to promote less scar formation and better patency than pure mechanical methods [Huikeshoven, 2002].

Since their development, laser techniques have supplanted the other methods and have become the standard for myocardial revascularization. There are now two approaches for laser revascularization: surgical and percutaneous. The surgical approach for TMR was described first and

generally involves a left anterior thoracotomy to permit direct application of the laser probe on the myocardium. Surgical TMR using minimally invasive techniques has also been reported [Trehan, 1998]. With the probe, a series of channels (approximately 25 to 40) are created transmurally from the epicardial surface [Saririan, 2003]. Digital pressure usually controls external bleeding, but sutures must sometimes be placed in the epicardium for hemostasis [Allen, 1999; Frazier, 1999].

More recently, percutaneous approaches to laser revascularization have also been developed. PMR employs catheter-based laser systems that are introduced into the left ventricle from the femoral artery. The laser probe is guided by fluoroscopy to the endocardium surface, where pulses are delivered to create channels [Saririan, 2003]. In contrast to TMR, which creates transmural channels from the epicardial surface, PMR devices operate from the endocardial surface and are designed to penetrate less than the full wall thickness [Saririan, 2003]. The typical PMR probe channel measures 5-6 mm deep in walls of at least 8 mm thickness [Saririan, 2003].

2.2 FDA and CMS Status

The CMS Coverage Issues Manual describes the indications for which TMR is covered by CMS. The following excerpt from the coverage manual describes the status of TMR coverage:

> …as a late or last resort for patients with severe (Canadian Cardiovascular Society classification Classes III or IV) angina (stable or unstable), which has been found refractory to standard medical therapy, including drug therapy at the maximum tolerated or maximum safe dosages. In addition, the angina symptoms must be caused by areas of the heart not amenable to surgical therapies such as percutaneous transluminal coronary angioplasty, stenting, coronary atherectomy or coronary bypass. Coverage is further limited to those uses of the laser used in performing the procedure which have been approved by the Food and Drug Administration for the purpose for which they are being used.
>
> Patients would have to meet the following additional selection guidelines:
>
> 1. An ejection fraction of 25% or greater;
> 2. Have areas of viable ischemic myocardium (as demonstrated by diagnostic study) which are not capable of being revascularized by direct coronary intervention; and
> 3. Have been stabilized, or have had maximal efforts to stabilize acute conditions such as severe ventricular arrhythmias, decompensated congestive heart failure or acute myocardial infarction.
>
> Coverage is limited to physicians who have been properly trained in the procedure. Providers of this service is performed must also document that all ancillary personnel, including physicians, nurses, operating room personnel and technicians, are trained in the procedure and the proper use of the equipment involved. Coverage is further limited to providers which have dedicated cardiac care units,

> including the diagnostic and support services necessary for care of patients undergoing this therapy. In addition, these providers must conform to the standards for laser safety set by the American National Standards Institute, ANSIZ1363 [CMS, 2004].

FDA-approved lasers and their uses are outlined in the next section of this report (Section 2.3).

PMR is not currently covered by CMS. The application for pre-market FDA approval for PMR was denied in March, 2004, though further efforts are ongoing to obtain FDA approval for the technology [CardioGenesis, 2004].

2.3 Current Technology

Three types of lasers have been examined in clinical trials: carbon dioxide (CO_2); holmium: yttrium-aluminum-garnet (Ho:YAG); and xenon chloride (XeCl) excimer. The latter two types may be used with fiber-optic catheters and therefore can be applied in percutaneous or thoracoscopic approaches [Abo-Auda, 2003]. The FDA has approved only Ho:YAG (CardioGenesis Corporation) and CO_2 lasers (PLC Medical Systems) for use with TMR.

2.3.1 CO_2 Lasers

These lasers were the first type used for TMR and operate in the infrared range of the light spectrum [Huikeshoven, 2002]. CO_2 systems cannot be

employed through optical fibers and therefore are limited to use in surgical TMR.

2.3.2 Ho: YAG Lasers

These lasers were the second type developed for TMR and deliver energy in the mid infrared range through an optical fiber [Huikeshoven, 2002]. Because these systems utilize an optical fiber, they may be employed with PMR in addition to TMR.

Three systems using Ho:YAG lasers (Biosense, Eclipse, CardioGenesis) have been examined in clinical studies of PMR, though to date none have been approved by the FDA. The Biosense system (Johnson & Johnson) does technically differ from the other two systems in that it lases from the endocardial surface, rather than from within the myocardium after physical puncture of the endocardium.

2.3.3 XeCl Excimer Lasers

Excimer lasers work in the ultraviolet range and are the least clinically tested type of lasers in this context [Huikeshoven, 2002]. These lasers have not been approved by the FDA.

2.4 Possible Mechanisms of Action

The possible mechanism of action for TMR and PMR remains controversial. As the open channel hypothesis has fallen by the wayside, the three most popular proposed mechanisms are angiogenesis, cardiac denervation, and the placebo effect.

As a comprehensive review of the experimental data is beyond the scope of this work, these potential mechanisms are described only briefly below.

2.4.1 Creation of Patent Endocardial Channels

The initial rationale for TMR and PMR was creation of patent channels from the left ventricular (LV) cavity to provide oxygenated blood directly to the myocardium. The data to support this mechanism are controversial, but the preponderance of experimental evidence refutes this hypothesis.

While some experimental studies have reported persistently patent channels in the days to weeks following TMR procedures, most pathologic studies have shown that clot formation causes occlusion of TMR channels within days of the procedure [Fisher, 1997; Hardy, 1987; Saririan, 2003;

Whitaker, 1999]. Moreover, most studies have shown no acute improvement in perfusion following TMR, which would be expected if patent channels were the predominant mechanism of action [Saririan, 2003; Whitaker, 1999].

In the weeks that follow, some of these channels may re-open, though the reason some open and others close is not known. Most studies involving follow up over several months have reported lack of channel patency [Huikeshoven, 2002; Whitaker, 1999], but a minority of studies has reported evidence for patent channels [Whitaker, 1999]. These few studies claiming patent channels have also reported significant recoil and dimunition of channel size from 1 mm at creation to 75 μm at follow up [Whitaker, 1999].

However, even if patency were maintained, investigators have argued that the channels created by TMR could not contribute in any meaningful way to perfusion. First, Pifarre and colleagues have shown that since LV cavity pressure is usually less than the intramyocardial pressure surrounding TMR channels, the latter could not be filled from the former [Huikeshoven, 2002; Pifarre, 1969]. Second, since the internal surface area of TMR channels is less than 0.01 percent of the capillary internal surface area, any

blood flow would contribute only minimally to oxygenation [Huikeshoven, 2002]. For these theoretical reasons, and because of the lack of significant clinical or experimental reasons in its support, this proposed mechanism of action has been largely abandoned.

2.4.2 Stimulation of Angiogenesis

Following TMR procedures, animal studies have shown increased vascular density within TMR scar [Huikeshoven, 2002; Whitaker, 1999]. These findings have led to the hypothesis that TMR may act by stimulating angiogenesis. TMR has been reported to upregulate vascular endothelial growth factor (VEGF) messenger ribonucleic acid (RNA) and increase expression of other growth factors [Horvath, 1999; Chu, 1999]. Whether this is a specific effect of laser irradiation or a non-specific response to tissue injury is unclear [Chu, 1999]. In either case, data regarding the extent of new vessel growth (whether confined to the TMR channels or extending into the surrounding tissue) have been controversial [Huikeshoven, 2002].

The angiogenesis hypothesis is indirectly supported by animal studies demonstrating no immediate post-procedure perfusion changes but an

improved blood flow after 4 to 26 weeks [Bridges, 2004; Huikeshoven, 2002]. Improved perfusion has been reported with all three available laser types in both canine and porcine models [Hughes, 2000; Huikeshoven, 2002; Martin, 2000; Yamamoto, 1998]. However, these findings have not been consistently replicated in humans. While some studies have reported better perfusion at follow up [Frazier, 1999], others have not demonstrated significant improvement [Allen, 1999; Burkhoff, 1999].

2.4.3 Myocardial Denervation

Because angiogenesis requires some time for new vessel growth, this mechanism cannot explain the angina relief that some patients may experience within days of treatment. One possible explanation for this acute pain relief is cardiac denervation. According to this hypothesis, the laser irradiation and consequent thermal tissue effects produce damage in the heart's sympathetic nerve fibers.

Several experimental studies have demonstrated destruction of cardiac nerve fibers with TMR at 2 to10 weeks [Arora, 2001; Huikeshoven, 2002; Kwong, 1997; Le, 2000; Yamamoto, 2000]. However, other experimental studies have not found evidence for denervation [Hirsch, 1999; Hughes,

1999]. In one porcine experimental study, there was evidence for regional denervation at 3 days post-operatively with re-innervation at 6 months [Hughes, 2004]. In one of the few clinical studies of denervation, Al-Sheikh and colleagues found that six of eight patients had positron emission tomography (PET) evidence for increased denervation defects following TMR [Al-Sheikh, 1999]. In 1-year follow-up exercise testing of patients who had originally been randomized to TMR or placebo and those randomized to PMR or placebo, Myers and colleagues found no echocardiographic evidence for increased silent ischemia in the TMR and PMR groups [Myers, 2002].

2.4.4 Placebo Effect

Because of the conflicting experimental and clinical evidence for a definite mechanism of action, a placebo effect has been proposed as the etiology for the angina relief seen in clinical studies. Clinical TMR studies cannot be blinded because of the ethical dilemmas associated with sham surgery, but one double-blinded, randomized trial of PMR has been performed. In this study, angina relief in the PMR group was significantly higher than in the sham group [Salem, 2004]. In contrast, a larger PMR study (n = 298) with a

different sham procedure showed no difference between groups [DIRECT, 2001].

2.4.5 Other

Besides the hypotheses described above, other proposed mechanisms of action for TMR include improved cardiac compliance because of scar formation and myocardial destruction allowing redistribution of blood flow [Huikeshoven, 2002].

2.5 Utilization

Although initially intended for patients not amenable to standard revascularization techniques, TMR has also been applied as an adjunct to conventional CABG or other cardiac procedures [Allen, 2000; Peterson, 2003]. The use of TMR as an adjunct to other cardiac revascularization is "off-label" from its current FDA indication.

In collaboration with the FDA and the Society of Thoracic Surgeons (STS), Peterson and colleagues reviewed the STS database for 1998 to 2001 to examine the use and safety of TMR in community practice [Peterson, 2003]. The STS database is a voluntary, multi-center clinical database that

collects information from two-thirds of US cardiothoracic hospitals and has patient, clinical, and acute outcomes data on more than 2.1 million cardiothoracic procedures [Peterson, 2003].

This review found that more combined procedures (2475 TMR plus CABG, 581 TMR plus other cardiac procedures such as valve surgery) have been performed than TMR-only procedures (661) [Allen, 2000; Peterson, 2003]. By 2001, 131 (36 percent) of STS sites were performing TMR with a median volume of 12 procedures (range 1 to 150) during the 4-year study period [Allen, 2000; Peterson, 2003].

3. METHODS

3.1 Overview of the Literature Search

A search of the MEDLINE and PubMed databases was conducted. The International Network of Agencies for Health Technology Assessment (INAHTA) database (www.inahta.org) and National Guideline Clearinghouse (www.guideline.gov) were searched for technology assessments and guidelines. Evidence-based medicine reviews and the Cochrane Central Register of Controlled Trials were searched to obtain additional reviews and trials not captured in the initial search. References from recent reviews and technology assessments were reviewed for additional pertinent articles.

A horizon scan was conducted by searching ClinicalTrials.gov (www.clinicaltrials.gov) and Current Controlled Trials (www.controlled-trials.com).

3.2 Literature Search Strategy

Due to the broad nature of the report and the relatively limited scope of the literature on the topic, we decided to conduct basic keyword searches,

limiting results by “English language” and “human subjects.” The search strategy was as follows:

Database: Ovid MEDLINE(R) <1966 to May Week 1 2004>

1 transmyocardial revascularization.mp. (123)

2 transmyocardial laser revascularization.mp. (321)

3 percutaneous myocardial laser revascularization.mp. (14)

4 percutaneous myocardial revascularization.mp. (19)

5 1 or 2 or 3 or 4 (427)

6 limit 5 to (human and english language) (263)

To limit the literature to the most useful and pertinent studies, the following criteria were used to exclude irrelevant abstracts:

- Study has fewer than 12 patients;
- Study does not have human subjects;
- Abstract is not in English;
- 30-day mortality is not reported.

3.3 Results of the Literature Search

The search of the MEDLINE and PubMed databases yielded 263 abstracts for review. Review of these abstracts produced 56 articles for full-text

review. Updated searches, review of references, and suggestions from AHRQ and peer reviewers uncovered an additional 19 articles. Full-text review utilized the same general exclusion criteria as were used during abstract review. Articles were categorized as RCTs or observational studies (which included cohort studies and case series). Inclusion criteria for the articles were as follows:

RCTs: Trial reports efficacy of TMR or PMR in terms of angina and/or survival.

Observational studies:

1. Surgical complications related to TMR or PMR are reported, including mortality and other serious complications such as tamponade, re-operation, and infection.
2. The nature of utilization of TMR or PMR is mentioned (i.e., alone vs. with CABG, patient eligibility criteria).

Two physicians – one an MD/PhD (methodologist), and the other an MD (cardiologist) – independently reviewed the articles and extracted general information on objectives, design, participants' age, and outcomes. Detailed information was extracted only from studies that met the major inclusion criteria, and data were collected on study design. RCT study

quality was assessed using the Jadad score [Jadad, 1996] modified to suit the technologies under consideration here (Appendix 8.3).

Observational study quality was assessed using the criteria described by Sackett [Sackett, 2000], also modified to more directly apply to the technologies at hand (Appendix 8.3). Disagreements were resolved by consensus, and a third physician was consulted to decide any remaining questions.

After applying inclusion criteria to the full-text articles, 38 publications, representing 14 RCTs, 21 observational studies, and three follow-up reports of other studies were included. These articles are described in the "Results" section below, with abstracted data provided in the evidence tables (Appendix 8.4).

Evidence tables for all included articles are provided in Appendix 8.4. Data abstracted from each article include:

- Study characteristics – including location, number of centers, type of laser used, number of channels created, whether enrollment was consecutive, and length of follow up.

- Patient characteristics – including number of subjects (men and women), mean age, race and angina class, inclusion and exclusion criteria, patient history, and physical examination findings.
- Results – including mortality (30-day and other time points), mean angina class, and other outcomes reported (such as improvement of two or more CCS classes, exercise time).
- Quality score – as described above, a quality score was assigned to each article, including any notes of important details of the study not captured elsewhere in the evidence table.

The horizon scan found no relevant studies to be currently underway.

3.5 Important Issues Considered

Two issues were considered by the authors of this review to be especially relevant to the evaluation of TMR and PMR and were given special attention in this evidence summary. First, the placebo effect is potentially powerful influence in response. The presence and nature of blinding are accordingly detailed in the evidence tables. Second, because of concern about a mechanism of action, each study was specifically examined for ancillary results that might shed light on this issue.

4. RESULTS

Of the 75 full-text papers reviewed, 38 (51 percent) met the inclusion criteria. Of these, 14 (37 percent) were RCTs and 21 (55 percent) were longitudinal observational studies (Table 1). Three observational studies included patients receiving TMR as sole therapy and TMR plus CABG. Three studies (eight percent) providing additional long-term follow-up information for included RCT papers are mentioned briefly with their primary paper summaries and have separate evidence tables in Appendix 8.4.

All studies together contributed a total of 3602 TMR procedures conducted alone, 3031 TMR procedures done with CABG, and 955 PMR procedures.

4.1 Efficacy – Randomized Clinical Trials

4.1.1 TMR

4.1.1.1 Overview

Seven trials of TMR versus medical therapy met the inclusion criteria. Two of those trials also have published extended follow-up data and these are included here as well.

Quality scores for the included studies were 2 or 3 (on a 4-point scale). No TMR study was double-blinded. Three were multicenter trials, and five included more than 100 patients. Mean age of the patients was between 60 and 64 years. Prior myocardial infarction was present in 64 percent to 80 percent of patients.

None of the TMR-versus-medical therapy trials indicated a benefit in terms of mortality at 1 year. The only benefit in significant survival following TMR as sole therapy compared to medical treatment was found in a 5-year follow up of one of the included trials. All trials showed statistically significant improvements in angina symptoms at 1 year and when assessed longer term. One trial demonstrated improved myocardial perfusion in some patients [Frazier 1999]. Two trials observed reductions in hospitalizations or of coronary events at 1 year [Allen, 1999; Frazier, 1999], and two indicated improved exercise time [Allen, 1999; Burkhoff, 1999]; others did not find those benefits. Four trials that evaluated quality of life (using the Duke Activity Status Index [DASI] or Seattle Angina Questionnaire [SAQ]) found significant improvements at 1 year [Allen, 1999; Frazier, 1999; Burkhoff, 1999; Schofield, 1999].

4.1.1.2 Summaries

Aaberge and colleagues [Aaberge, 2000] reported the results of a single-center Norwegian trial in which 100 patients with refractory angina not amenable to traditional revascularization were randomized to receive TMR or medical therapy. A CO_2 laser was used. Of the patients randomized to TMR, 76 percent were in New York Heart Association (NYHA) class III, and 24 percent were in NYHA class IV. These authors found no improvement in 30-day or 12-month mortality. Thirty-day mortality was four percent in the TMR group and zero percent in the control group. Twelve-month mortality was 12 percent and eight percent, respectively. At 1 year, 39 percent of the TMR patients experienced an improvement of two or more NYHA functional classes compared with zero percent of the medically treated group. With regard to other outcomes, there was no evident difference between TMR and medically treated patients in total exercise time or maximal oxygen consumption. However, time to chest pain was significantly longer in TMR versus medically managed patients, and angina was reported as an exercise-limiting factor in significantly fewer TMR than medically managed patients (62 percent vs. 76 percent).

In a follow up of the same group of patients, Aaberge and associates reported 32-month to 60-month outcomes (mean 43 months) [Aaberge, 2002]. Again, no benefit was noted in mortality, which was 24 percent in the medical therapy group and 22 percent in the TMR. However, 60 percent of the TMR patients were in NYHA class I or II, whereas 16 percent of the medically treated patients were in class II or III (none were in class I). Twenty-four percent of patients in the TMR group improved by two or more NYHA functional classes compared with three percent of the medically treated patients.

Allen and coworkers [Allen, 1999] reported a 275 patient RCT in which Ho:YAG laser TMR was compared with medical therapy. All patients were reported to have medically refractory CCS class IV angina. Under an FDA-approved protocol, a priori criteria were prospectively defined to permit crossover of medically managed patients, allowing unstable patients to receive TMR. Thirty-day mortality was similar in both groups: five percent in the TMR group and two percent in the control group. One-year Kaplan-Meier survival was similar between TMR (84 percent) and medically managed (89 percent) patients. After 12 months of follow up, 76 percent of the patients in the TMR group and 32 percent of the patients treated

medically had a reduction in angina of two or more CCS classes. Angina improvement in crossover patients was similar to that observed for patients randomized to TMR. Cardiac-related re-hospitalization was less common in the TMR group (33 percent) than in the medically treated group (61 percent). Patients randomized to TMR also had a significantly greater exercise tolerance (5.0 vs. 3.9 metabolic equivalents). A significant improvement was also noted in quality-of-life scores and rates of cardiac-related re-hospitalization.

Recently, a 5-year follow up of this work has been reported [Allen, 2004]. Long-term survival was significantly increased in patients randomized to TMR versus patients randomized to medical therapy (65 percent vs. 52 percent) and was found to be significantly predicted by 1-year angina improvement in TMR patients. Reductions in angina of two or more classes were found in 88 percent of the TMR group, compared to only 44 percent of the medical treated patients.

Burkhoff and associates [Burkhoff, 1999a] performed a prospective, multicenter, RCT of Ho:YAG laser TMR compared with medical therapy. One hundred eighty-two patients from 16 centers in the United States were

randomly assigned to undergo TMR (n = 92) or medical management (n = 90). All subjects had CCS class III or IV angina (38 percent class III, 62 percent class IV). Operative mortality rate was low (one percent), while 12-month mortality was similar for TMR (five percent) and medically treated patients (10 percent). At 12 months, 52 percent of TMR and 86 percent of medically treated patients had CCS class III or IV angina. In addition, TMR was associated with statistically significant greater exercise tolerance and better quality of life as compared with medical therapy.

Frazier and colleagues published the results of an RCT conducted in 12 US Centers. Patients where randomized to CO_2 laser TMR or medical therapy and followed for 12 months [Frazier, 1999]. Sixty-nine percent of the patients assigned to TMR and 63 percent of the patients assigned to medical therapy had CCS class IV angina. Sixty (60 percent) of the medically treated patients who developed unstable angina crossed over to TMR therapy. Angina reduced two or more CCS classes for 72 percent of the patients in the TMR group and 13 percent of patients receiving the medical therapy. Although total survival was not different in the treatment arms at 30 days (three percent vs. seven percent) or 12 months (15 percent vs. 21 percent), event-free survival was higher in TMR patients

compared to medically managed patients at 1 year (66 percent vs. 11 percent). Survival free of cardiac events was defined as freedom from death, Q-wave myocardial infarction, cardiac-related hospitalization, and subsequent revascularization. The percentage of myocardial segments with fixed or reversible perfusion defects was assessed at 12 months using thallium 201 single-photon emission computed tomographic (SPECT) imaging. This percentage decreased by an average of 20 percent in the TMR group and worsened by 27 percent in the medical treatment group. Patients in the TMR group had a greater improvement (38 percent) in their quality of life than patients in the medical treatment arm (six percent). Admissions for unstable angina were two percent in the TMR group and 40 percent in the medical group. Angina was improved by two or more classes in 72 percent of the patients receiving TMR and in 13 percent of those receiving medical therapy.

Huikeshoven and colleagues have reported the results of a Dutch single-center trial. Thirty patients were randomly assigned to receive XeCl TMR or medical therapy [Huikeshoven, 2003]. No differences in survival were identified. No deaths were reported for the medically managed patients in the 12-month follow up, while TMR patients had a seven percent 12-month

mortality. Quality-of-life scores (EuroQol, SF-24, SAQ) were significantly better in the TMR group than in the control group.

Jones and colleagues [Jones, 1999] performed an RCT in a single US center. In this trial, 86 patients were assigned to receive either Ho:YAG TMR or medical therapy. All had advanced cardiac ischemia with CCS class III or IV angina, took at least two cardiac medications at maximum doses, and were ineligible for angioplasty or bypass. Twelve-month survivals were the same (12 percent) for both groups. At 1 year TMR patients had lower mean angina class than control patients (1.71 ± 0.2 vs. 3.86 ± 0.05). Exercise tolerance time at 1 year was better in TMR patients than control group patients (490 ± 17 seconds vs. 294 ± 12 seconds).

Schofield and colleagues [Schofield, 1999] reported a single-center, prospective, randomized trial in which 188 patients were randomly assigned to CO_2 laser TMR or medical therapy. Mortality at 30 days was zero percent in the control group and five percent in the TMR group, while at 12 months it was 11 percent in the TMR group and four percent in the medically treated group, although the differences in mortality were not statistically significant. The authors reported significantly less severe

angina symptoms in the TMR group. Twenty-five percent of the TMR group but only four percent of the medical group had a reduction of two or more CCS classes. At 1 year, investigators identified a doubling of the fixed defects in the medically managed group and no increase in fixed defects in the TMR group. There were, however, no significant differences in exercise capacity.

4.1.2 TMR with CABG

4.1.2.1 Overview

Only one study was identified in this category. This multicenter trial had a quality score of 3 (of a possible 4). This trial has extended follow-up data after the first publication, which is in press for publication in August 2004.

4.1.2.2 Summaries

Allen and colleagues [Allen, 2000] reported a US multicenter trial in which 263 patients whose standard of care was CABG and who had one or more ischemic areas not amenable to bypass grafting were prospectively randomized to receive CABG plus TMR to areas not graftable (n = 132) or CABG with non-graftable areas left unrevascularized (n = 131). Mean age of these patients was 64 years; 34 percent had previous myocardial

infarction, and mean EF was 51 percent. The operative mortality rate after CABG plus TMR was 1.5 percent versus 7.6 percent after CABG alone, although the Parsonnet-predicted mortality risk was comparable (6.3 percent, CABG plus TMR vs. 6.6 percent, CABG alone). One-year survival (95 percent vs. 89 percent) and freedom from major adverse cardiac events defined as death or myocardial infarction (92 percent vs. 86 percent) favored the combination of CABG plus TMR. Baseline to 12-month improvement in angina and exercise treadmill scores was similar between groups.

A follow-up study of the above trial assessed the long-term results of 218 of the original 263 patients (83 percent) [Allen, in press]. Kaplan-Meier survival up to 6 years was similar between CABG/TMR and CABG alone patients (76 percent vs. 80 percent). Using an intention-to-treat analysis based on independent blinded assessments, the 5-year follow up indicated that both groups experienced significant angina improvement from baseline; however, compared with patients receiving CABG alone, the TMR-plus-CABG group had a statistically lower mean angina score (0.4 ± 0.7 vs. 0.7 ± 1.1), a statistically lower proportion of patients with class III or IV angina (0 percent [0/68] vs. 10 percent [6/60]), and a trend towards

greater number of angina-free patients (78 percent [53/68] vs. 63 percent [38/60]).

4.1.3 PMR

4.1.3.1 Overview

The search identified six publications that report results of RCTs of PMR that met the inclusion criteria. One study, however, included some patients that were also included in other trials. Quality scores ranged from 2 to 4 (of a possible 4). Notably, three trials were double-blinded [Leon, 2004; Salem, 2004; Stone, 2002]. None of the reports reviewed showed improved mortality, and four indicated angina relief. Other benefits found in some trials were quality of life and exercise time.

One study was conducted at a single center, another included patients just from two centers, and the other three were multi-center. Each study included more than 100 patients.

Mean age ranged from 61 to 65 years. Prevalence of prior myocardial infarction ranged from 63 percent to 72 percent of patients. All patients included had angina class III or IV.

Of the three double-blinded PMR trials, no relative improvement in angina was found in two [Leon, 2004; Stone, 2002], while significant benefit was identified in one [Salem, 2004]. As noted below in the summaries, studies of PMR are heterogeneous with regard to patient population (e.g., presence of bypassable lesions), equipment/procedures used, and follow-up approach.

4.1.3.2 Summaries

Gray and colleagues [Gray, 2003] reported data from a single-center UK trial in which 73 patients were randomized to receive either PMR or medical therapy. Twenty-one of those patients were included also in the Potential Class Improvement from Intramyocardial Channels (PACIFIC) trial (see below). Inclusion criteria were: stable angina pectoris (class III or IV), unsuitable for conventional revascularization, evidence of reversible ischemia by thallium-201 scintigraphy, EF of $\geq$ 25 percent, and myocardial wall thickness $\geq$ 8 mm. Patients were followed up at 3, 6, and 12 months. The primary end point was exercise time. Secondary end points included angina scores, LVEF, quality of life, changes in medical therapy, and hospitalizations. No peri-procedure deaths occurred among the 36 patients

randomized to PMR, while 12-month mortality was three percent for both groups. At 12 months, exercise times were higher by 109 seconds in the PMR group, but lower by 62 seconds in the control group. Angina scores improved by two classes in 36 percent of PMR-treated patients at 12 months compared with zero percent of the control patients. Quality of life according to the SAQ was significantly better in PMR subjects.

Leon has reported the results of a 298 patient RCT of the Biosense PMR system versus medical therapy. Patients with functional class III or IV were divided into three arms (placebo = 102, low dose = 98, high dose = 98). Low-dose patients received 10-15 channels/zone and high-dose patients received 20-25 channels/zone. The 102 patients in the placebo group received a sham procedure. No crossovers were allowed. Mortality was similar among the groups. Major adverse cardiovascular event-free survival at 30 days significantly favored the placebo arm. No difference in improvement in functional classes (i.e., by two or more classes) was observed among the three groups. Exercise duration among the three groups was not significantly different. In terms of magnitude of ischemia, as assessed with SPECT, no consistent differences that would suggest a therapeutic effect were noted.

Oesterle and colleagues have reported the results of the PACIFIC trial [Oesterle, 2000]. In this trial, investigators randomly assigned 221 patients with refractory angina (135 class III and 86 class IV) and reversible perfusion defects on thallium stress testing to either PMR with continued medical treatment or to medical treatment alone. A total of 11 patients died during the follow-up period (eight PMR, three control). Overall survival showed no significant difference between the groups. In the PMR group, exercise duration increased by a median of 89 seconds as compared with an increase of 12.5 seconds in the control group. In addition, the CCS class assigned by the investigators decreased by at least two classes in 46 percent of patients assigned to PMR compared with only 11 percent of control patients. Quality of life, measured using the SAQ, was significantly better in the PMR than in the medically treated group at 1 year. As with all trials, assignment of anginal class was not blinded. Notably, the investigators examined ways in which this may have introduced bias by comparing the investigators' assessments of angina class with those made by an independent panel without knowledge of treatment assignment. Results indicated that study investigators assigned significantly lower CCS scores to PMR patients than did the blinded panel. However, grades from

the blinded panel were still significantly lower with PMR than with medical therapy.

Recently, Salem and colleagues reported results of the Blinded Evaluation of Laser Intervention Electively for Angina Pectoris (BELIEF) trial, a Norwegian RCT involving two centers [Salem, 2004]. A total of 82 patients were randomized to PMR using the Eclipse system or to a sham procedure and were followed for improvement in CCS functional class, exercise tolerance, and quality of life. An exclusion criterion in this trial was unstable angina requiring hospitalization within 14 days of change of medication. More than 80 percent of patients were in functional class III at baseline. There were no deaths in the PMR group through 1 year, with two deaths in the sham group (4.8 percent). This difference was not statistically significant. At 6 months, 41 percent of patients in the PMR group improved by two or more CCS classes compared with only 13 percent in the control group. There was no significant difference in exercise duration between the two groups, although patients in the control group had a faster onset of chest pain. Furthermore, there appeared to be a mild improvement in quality-of-life scores in favor of the PMR group.

Stone and colleagues have reported the results of the Prospective, Multicenter, Randomized trial of PMR in Patients with Nonrecanalizable Chronic Total Occlusions [Stone, 2002]. A total of 141 patients with class III to IV angina and a non-recanalizable chronic total occlusion were randomized to either PMR with the Eclipse system or to maximal medical therapy. Randomization took place after an unsuccessful, uncomplicated attempt to cross the chronic occlusion. Blinding was achieved through heavy sedation, dark goggles, and the concurrent performance of PCI in all patients. To assess the adequacy of blinding, patients completed a questionnaire before discharge regarding their belief about treatment assignment. Symptom-limited stress testing was performed at baseline and at 6 months. No significant differences between control and intervention were found for mortality (nine percent in both groups), angina class improvement, or revascularizations. The primary end point was the change in total exercise time from baseline to follow up. Exercise time improved by 62 seconds in the PMR group and by 54 seconds in the medical therapy group; however, this was not statistically significant.

Whitlow and colleagues have published the results of an RCT involving 330 patients with class III or IV rejected for conventional revascularization.

Subjects were randomized to receive either PMR using the Eclipse system or maximum medical therapy or [Whitlow, 2003]. Patients were followed up at 3, 6, and 12 months. Mortality was similar between groups at 1 year (7.9 percent, PMR vs. 6.7 percent, medical therapy). Patients who underwent PMR had statistically greater improvements in exercise duration (mean change from baseline 100 seconds longer for PMR vs. 20 seconds shorter for medical therapy). PMR patients' angina classification improved significantly, as well as the proportion of patients with an improvement of at least two functional classes at 1 year (38 percent vs. 19 percent). Quality of life, measured using the DASI, was significantly better for PMR patients at 1 year.

4.2 Safety and Utilization – Observational Studies

4.2.1 TMR

4.2.1.1 Overview

Fifteen observational studies satisfied inclusion criteria for this review. These studies reflected experience with over 2300 procedures. Eleven of the studies reported single-center data. Two studies analyzed data obtained from registries.

In terms of length of follow up, two studies, including one of the registry studies, followed patients to 30 days only. Thirteen studies followed patients up to 1 year. One study evaluated outcomes to a mean of 5 years. Mean patient age ranged from 57 to 67 years.

Short-term (30-day) mortality ranged from three percent to 15 percent. One-year mortality ranged from 15 percent to 26 percent. Beyond this, Schneider and colleagues [Schneider, 2001] reported a 36 percent mortality at 36 months, and, based on 5-year follow-up of a large multicenter observational study, Horvath noted a 42 percent mortality [Horvath, 2003].

Four of these observational studies included data both for patients who received TMR as sole therapy or TMR combined with CABG [Burns, 1999; Guleserian, 2003; Peterson,2003; Schneider, 2001].

Two of the studies were based on registries that allowed examination of trends and outcomes in community practice. Both were the largest in terms of number of cases included and participating centers. One of the registries was conducted outside of the US and prior to the randomized trial

experience. The other registry was retrospective, involving passive 30-day reporting from sites that participated voluntarily.

Some differences between the characteristics of included patients were identified between these two works and the other works. The percentage of patients in angina class III or IV was approximately 75 percent, while in other observational studies nearly all were in the most severe angina classes. (As noted above, randomized controlled trials used angina class III/IV as an inclusion criterion.) Another apparent difference in the patients reported in observational studies compared to patients in clinical trials is that LVEF is slightly lower and unstable angina more prevalent.

Though these studies were not examined specifically for evidence of treatment efficacy, before/after comparisons often showed reductions in angina score. Of the 15 studies identified, 10 showed an improvement in angina symptoms, and only three of them could not identify significant differences from baseline through follow up. Improvement in angina symptoms tended to be higher at 6 months, persisting usually at least 12 months. TMR has also been associated in those works with improvements

in quality of life, decreased medication usage, reduced hospital admissions, and improved exercise tolerance.

4.2.1.2 Summaries

Two reports were based on information extracted from TMR registries. Peterson and colleagues identified 3717 patients receiving TMR using either the FDA-approved CO_2 or Ho:YAG laser system at 173 US hospitals participating in the STS National Cardiac Database [Peterson, 2003]. From 1998 to 2001, the number of sites performing TMR increased from 33 (seven percent of total STS sites) to 131 (36 percent of total). The volume of procedures per site also increased during this period. Overall mortality rate of TMR as sole procedure was 6.4 percent. Operative risks were significantly higher in those patients with recent myocardial infarction, unstable angina, and depressed ventricular function. Patients without recent myocardial infarction, unstable angina, or depressed ventricular function had an operative mortality rate of 3.7 percent.

Burns reported data from 16 of the 22 centers in Europe and Asia registered with the Transmyocardial Laser Revascularization International Registry using a CO_2 laser [Burns, 1999]. Data were collected prior to the

US randomized trials to support FDA approval. TMR operative details were available on 932 patients. One hundred and seventy-seven cases had TMR combined with CABG, and 11 with percutaneous transluminal coronary angioplasty (PTCA). There was a high variation across centers in reporting information and follow up. In-hospital death rate was 9.7 percent. Other early complications were consistent with similar cardiothoracic surgical procedures. There was a decrease of two or more CCS angina classes in 47.3 percent, 45.4 percent, and 34·0 percent of survivors at 3, 6, and 12 months follow up, respectively. Preoperative treadmill exercise time was 6 minutes. This increased by 42 seconds at 3 months, 1 minute 43 seconds at 6 months, and 1 minute 50 seconds at 12 months.

Agarwal and colleagues have reported results from 102 patients who underwent isolated TMR using an CO_2 laser at a single center in India [Agarwal, 1999]. The early mortality was 15 percent. At 1 year there was significant improvement in angina class and effort tolerance, but no significant change in LVEF; mortality at 12 months was 17 percent.

Allen and colleagues presented information on 42 patients with refractory angina who received Ho:YAG TMR, were not candidates for PTCA or

CABG, had either CCS class IV angina (n = 23) or unstable angina (n = 19), and were unable to be weaned from intravenous nitroglycerin [Allen, 1998]. Peri-operative mortality was 12 percent, with no late deaths. At 3-month (n = 33) and 6-month (n = 21) follow up the mean angina class was 1.5 ± 0.1 and 1.1 ± 0.1, respectively.

Burkhoff and colleagues [Burkhoff, 1999b] assessed outcomes of 132 patients with severe angina who underwent TMR as sole therapy with a CO_2 laser in a single center. Approximately half of the patients enrolled had unstable angina. Thirty-day and 12-month mortality were, respectively, 12 percent and 22 percent.

Dowling and colleagues have reported outcomes of Ho:YAG TMR performed in 85 class IV patients, all with unstable angina, at 14 centers [Dowling, 1998]. Operative mortality was 12 percent, and 12-month mortality was 22.4 percent. At 3 months, 86 percent of patients had class II angina or better. At 6 and 12 months, 77 percent and 75 percent of patients, respectively, had class II angina or better. Mean angina class at 6 months was 1.5 ± 1.1 and was 1.6 ± 1.3 at 12 months.

Hattler and colleagues reported outcomes of CO_2 TMR performed in 76 patients with unstable angina and compared their outcomes with 91 stable patients receiving TMR during the same period [Hattler, 1999]. Operative mortality was 16 percent in unstable patients and three percent in stable patients. One-year mortality was 26 percent in unstable patients and 14 percent in stable patients; however mortality between 30 days and 1 year was similar between groups (13 percent and 11 percent). Significant improvement in angina class (two or more classes from baseline) was observed in patients who received TMR while unstable at 3 months (69 percent), and at 6 and 12 months (82 percent and 82 percent), and was similar to stable patients who received TMR.

Horvath and coworkers [Horvath, 1997] presented data from 200 patients at eight US hospitals. TMR was used as the sole therapy for patients with ischemic heart disease not amenable to PTCA or CABG. TMR was performed with a CO_2 laser. The patients were followed for a combined 1560 months (mean 10 ± 3 months per patient). Their mean age was 63 years and their EF was 47 percent. The peri-operative mortality was nine percent. Angina class decreased significantly from before treatment to 3, 6, and 12 months. A significant decrease in the number of perfusion defects

in the treated LV free wall was observed, as well as a decrease in the number of admissions for angina in the year after the procedure when compared with the year before treatment. Recently, Horvath and colleagues have published a 5-year follow up. From the original enrolment, patients who were lost, died, or received an additional revascularization procedure were excluded for this analysis. The results for the remaining group of 78 show that after an average of 5 years, the average angina class significantly improved to 1.6 ± 1. Sixty-eight percent of patients experienced a decrease in angina of at least two classes, and 17 percent were angina-free. Five-year SAQ scores revealed an average improvement of 170 percent over the baseline results.

Nagele and colleagues reported the results of a total of 60 patients who suffered from refractory angina that could not be revascularized by conventional methods who were suggested for TMR [Nagele, 1998]. Sole TMR was performed with a CO_2 laser. In 126 candidates for the procedure, their refractory status was confirmed by checking antianginal medication and increased when possible. Patients were reevaluated between 1 and 2 months later. The decision to proceed with the TMR was then made. Medical management by intensification of drug treatment was possible in

about 50 percent of patients initially submitted for TMR. After 3 months the CCS fell from 3.31 $\pm$ 0.51 to 1.84 $\pm$ 0.77 in 49 patients, but increased in the total group to 2.02 $\pm$ 0.92 after 6 months (n = 47), to 2.26 $\pm$ 0.99 after 1 year (n = 42), to 2.47 $\pm$ 1.11 after 2 years (n = 38), and to 2.58 $\pm$ 0.9 after 3 years (n = 19). MIBI/PET data at rest and after 6 months was worse in the TMR group. The peri-operative mortality was 12 percent. Mortality after 1 and 3 years was 23 percent and 30 percent, respectively. There was a high rate of cardiac events and new procedures.

Guleserian and coworkers [Guleserian, 2003] reported during a 24-month period 81 consecutive high-risk patients at a single center who underwent either sole therapy TMR (n = 34) or TMR with CABG (n = 47) using a Ho:YAG laser. High-risk patients were considered as those with EF ≤ 40, unstable angina, or congestive heart failure. Patients were demographically similar, except that sole TMR therapy patients were more likely to have had prior CABG than were CABG plus TMR or CABG-alone patients (96 percent, 24 percent, and 15 percent, respectively) and a significantly higher incidence of prior myocardial infarction (75 percent, 56 percent, and 35 percent, respectively). For sole therapy TMR, quality of life was diminished comparing TMR with CABG and CABG only. In the TMR

group, 30-day mortality was nine percent; after CABG plus TMR, it was four percent.

Schneider and colleagues [Schneider, 2001] assessed outcomes of 41 patients at a single center in Germany who underwent TMR using a Ho:YAG-laser, 14 as TMR alone and 27 with additional CABG. Follow up was obtained at 6, 12, 18, 24, and 36 months in this prospective study. Only 50 percent of TMR alone patients (n = 8) and 22 percent of combined TMR and CABG patients (n = 6) were available for long-term follow up. TMR CCS class improved up to 18 months postoperatively, and after 24 and 36 months postoperatively there was absence of a positive effect of TMR: the CCS class decreased to 2.4 as compared to 3.5 preoperatively. After a combined CABG and TMR there was a significant decrease in angina at all times. The CCS functional class in these patients was 1.7 at 36 months as compared to 3.5 preoperatively. There was no significant change in exercise tolerance as compared to preoperatively. LVEF did not improve in either of the groups. Thallium scintigraphy indicated no improvement in myocardial perfusion in laser treated areas. Mortality rates at 36 months were 36 percent in the TMR group and 11 percent in the combined TMR plus CABG group.

Five trials have reported information from 21, 34, 34, 15, and 16 patients, respectively, at single centers who received TMR as sole therapy [Cooley, 1996; De Carlo, 2000; Landolfo, 1999; Lee, 2000; Muxi, 2003]. Thirty-day mortality in those studies ranged from three percent to 10 percent. Twelve-month mortality was 13 percent to 24 percent. All these studies identified angina improvements in patients receiving TMR. In the study by Landolfo and colleagues, despite the lack of demonstrable improvement in myocardial perfusion, TMR improved symptoms, although the maximal improvement was seen at 6 months post-TMR. Muxi and colleagues reported a significant decrease in angina at 3, 6, and 12 months from baseline, with a significant improvement in myocardial perfusion in laser-treated areas.

4.2.2 TMR with CABG

4.2.2.1 Overview

Six observational studies of TMR plus CABG met the inclusion criteria. Four of them reported data on patients who received CABG plus TMR together with data on patients who received only TMR. Mean age in these studies ranged from 61 to 65 years. Previous myocardial infarction was

reported in 50 to 77 percent of patients. Fifty-eight to 100 percent of patients had angina class III/IV, and EF ranged from 33 to 51 percent.

4.2.2.2 Summaries

Gregoric and colleagues [Gregoric, 2003] reported data on 17 patients who underwent TMR CO_2 laser combined with CABG. The patients had a mean age of 63 years and a mean EF of 33 percent. All but one patient had undergone previous coronary surgery. The mean follow-up period was 6.2 months. One patient died. At follow-up examination after a mean of 6 months (range, 2 to 9 months), 15 patients remained free of angina and one had mild angina. None had required further hospitalization.

The 47 high-risk patients assessed in the single-center study conducted by Guleserian and colleagues experienced a four percent 30-day mortality [Guleserian, 2003].

Peterson and colleagues analyzed the STS registry reported data from 2475 patients who received TMR combined with CABG [Peterson, 2003]. Overall operative mortality in this group was 4.2 percent. When considering patients without recent myocardial infarction, unstable angina,

or depressed LVEF, the operative mortality rate was 2.6 percent. This study also compared 390 patients in the STS database who received CABG plus TMR with a control group created from 39,000 CABG-only patients with triple-vessel disease who received fewer than three grafts. Operative mortality was similar between groups.

Stamou and colleagues [Stamou, 2002] have reported the results of 30-day and 3-, 6-, and 12-month clinical follow-up after CABG plus Ho:YAG or CO_2 TMR in a consecutive series of 169 patients with refractory angina pectoris and at least one myocardial ischemic area not amenable to CABG. One-year survival and event-free survival were 85 percent and 81 percent, respectively. At the end of the first year after the procedure, seven patients (four percent) had angina class III/IV versus 152 patients (90 percent) at baseline.

Long-term mortality (36-month) identified by Schneider and colleagues in a group of 27 patients was 11 percent [Schneider, 2001]. There was a significant decrease in angina at all times. The CCS functional class in these patients was 1.7 at 36 months as compared to 3.5 preoperatively.

Wehberg and colleagues have published the results of a single-center retrospective analysis of 6-month follow up of 255 consecutive patients who received either CABG alone (n = 219) or CABG and TMR (n = 36). TMR was performed in non-graftable regions. Patients had CCS angina scores III or IV and EF ≥ 30 percent. Age and EF were similar for both groups, although a significantly higher percentage of patients in the CABG group had congestive heart failure (28 percent vs. eight percent). One-month mortality was similar in both groups (2.3 percent in postoperative angina scores were similar in both groups. the CABG group and zero percent in the CABG plus TMR). Other major adverse outcomes were also similar in the two groups. One-month

4.3.2 PMR

4.3.2.1 Overview

Two observational studies of PMR were identified. Mean age was 61 and 62 years, prior myocardial infarction was present in 60 percent and 68 percent of patients, and mean EF was 38 percent and 48 percent. Only one of these studies reported baseline angina class. Both studies report 6-month follow up. No deaths were reported during this period in either study.

4.3.2.2 Summaries

Kaul and colleagues reported information from 35 patients from a single center in India with zero percent mortality after a 6-month follow up after PMR treatment with the Eclipse device [Kaul, 1999]. All patients were reported to have class III or IV angina prior to PMR; at 3 months mean angina class was 0.94 ± 0.65, and at 6 months mean angina class was 1.08 ± 0.58.

Kornowski and colleagues presented data from 77 patients treated at three US hospitals with PMR using the Biosense device [Kornowski, 2000]. There were no deaths at 6 months. Exercise duration significantly increased from 387 ± 179 seconds at baseline to 479 ± 161 seconds at 6 months. The time to onset of angina increased significantly from 293 ± 167 seconds at baseline to 414 ± 169 seconds at 6 months. Time to ST-segment depression (greater than 1 mm) also increased significantly from 327 ± 178 seconds at baseline to 436 ± 175 seconds at 6 months. Angina by CCS class improved from 3.3 ± 0.5 at baseline to 2.0 ± 1.2 at 6 months.

5. CONCLUSIONS

TMR has been evaluated in seven clinical trials; all seven studies report significant improvement in the frequency and/or severity of angina after TMR, with no net improvement in survival. Two trials with prolonged follow up suggest that symptomatic improvement is persistent, although other studies demonstrate a trend towards diminished relief after the first 6 months following TMR. The only benefit in survival following TMR as sole therapy compared to medical treatment has been found in a 5-year follow up of a multicenter, randomized experience. In addition to symptomatic relief, TMR was associated with an increase in exercise tolerance and quality of life. There were no consistent trends regarding the impact of TMR on admission for unstable angina, reduction in antianginal medications, cardiac events, or other complications (in particular congestive heart failure that might follow myocardial tissue damage due to therapy).

Any symptomatic benefit of TMR appears to be out of proportion to demonstrable improvement in myocardial perfusion. Only one of three trials that examined myocardial perfusion demonstrated some improvement in perfusion after TMR.

Only one trial assessed the benefit of TMR plus CABG; this suggested that the addition of TMR significantly reduced mortality without influencing anginal symptoms. Although both groups realized significant angina relief through 1 year, 5-year follow up indicated that CABG plus TMR provided superior angina relief compared to CABG alone. Regarding the 12-month survival benefit, it appeared to be explained entirely by the lower rate of 30-day mortality in TMR plus CABG vs. CABG alone patients (1.5 percent vs. 7.6 percent).

Both clinical trials and observational studies provide information on the adverse effects of TMR. In clinical trials, 30-day mortality was variable, up to five percent. In observational studies, 30-day mortality was up to 15 percent, with 12-month mortality ranging between 13 percent and 25 percent. Risks appear to be higher in those patients with recent acute cardiac events, unstable angina, and depressed ventricular function.

In addition, there are some data from observational studies regarding utilization of the procedure. Notably, TMR – a procedure intended as palliative therapy for advanced refractory coronary disease – is frequently

used for less severe patients in community practice. Approximately 25 percent of patients have angina that is not severe enough to satisfy FDA labeling requirements or Medicare coverage criteria for use of TMR.

Although the evidence is not as consistent, PMR trials suggest that the procedure can improve angina symptoms; this finding was reported in four of six trials. As with TMR, there is no evidence of physiological changes or increases in survival.

The available studies have notable limitations. These include:

- Lack of a clear definition of "maximal medical therapy" prior to inclusion in a study and in the control arm of clinical trials. It appears that a significant proportion of patients initially referred for TMR with refractory angina can be stabilized medically.
- Frequent treatment crossovers. In two major trials, Frazier and colleagues and Allen and colleagues allowed crossovers from the medical therapy group to the TMR group. In the Frazier trial, crossover was allowed as "an incentive for patients assigned to maximal therapy to remain in the study if medical therapy failed."

- Frequent lack of blinding in outcomes assessment. This could lead to an apparent increased therapeutic effect of TMR/PMR. Though it is evidently difficult (though not impossible) to blind patients to their treatment, it is feasible to blind the individual responsible for assessing trial outcomes, as was done in blinded validations of two trials at 1 year and in the randomized long-term follow-up studies.
- Presence of a placebo effect. This is likely to be a powerful factor in an intervention such as TMR or PMR, particularly in early follow up.

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8. Appendices
Appendix 8.1 Glossary

Abbreviations used in the text

AHRQ	Agency for Healthcare Research and Quality
BELIEF	Blinded Evaluation of Laser Intervention Electively for Angina Pectoris
CABG	Coronary artery bypass grafting
CCS	Canadian Cardiovascular Society
CMS	Centers for Medicare and Medicaid Services
CO_2	Carbon dioxide
DASI	Duke Activity Status Index
ECG	Electrocardiogram
EF	Ejection fraction
FDA	Food and Drug Administration
Ho:YAG	Holmium:yttrium-aluminum-garnet
INAHTA	International Network of Agencies for Health Technology Assessment
J	Joule
LV	Left ventricle (or ventricular)
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
mm	Millimeter

μm	Micrometer
NR	Not reported
NYHA	New York Heart Association
PACIFIC	Potential Class Improvement from Intramyocardial Channels
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PMR	Percutaneous myocardial laser revascularization
PTCA	Percutaneous transluminal coronary angioplasty
QoL	Quality of life
RCT	Randomized controlled trial
RNA	Ribonucleic acid
SAQ	Seattle Angina Questionnaire
SPECT	Single-photon emission computed tomography
STS	Society of Thoracic Surgeons
TMR	Transmyocardial revascularization
VEGF	Vascular endothelial growth factor
XeCl	Xenon Chloride

Appendix 8.2 Study Summary Tables

TMR alone

Table 1. Characteristics of RCT studies of TMR alone

Author	N	# centers	Mean age (yrs)	Quality Score (out of 4)	Previous MI (%)	III/IV (%)	LVEF (%)	30- d mortality (%)	12 m mortality (%)	Long term mortality (%)	Angina	Other
1. Aaberge	100	1	63	2	70	100	49	4	12	23% (32-60 month)	+	Hospital, Exercise
2. Allen	275	18	60	2	64	100	47	5	16	35% (5 year)*	+	Events, QoL, Excercise
3. Burkhoff	182	16	64	3	70	100	50	1	5	NR	+	NR
4. Frazier	192	12	61	1	80	100	50	3	15	NR	+	Events, Perfusion, QoL
5. Huikeshoven	30	1	63	1	NR	NR	55	0	7	NR	+	QoL
6. Jones	86	1	62	2	68	NR		2	12	NR	+	Exercise
7. Schofield	188	1	60	2	74	100	48	5	11	NR	+	Exercise
Total	1053											

*** p = 0.05 Mortality in the TMR group compared with mortality in the control group.**

Table 2. Characteristics of Observational studies of TMR alone

Author	N	# centers	Mean age (years)	Previous MI (%)	III/IV (%)	LVEF (%)	30-d mortality (%)	12-m mortality (%)	Angina
1. Agarwal	102	1	57	32	54	45	15	17	ND
2. Allen	42	1	62	69	100	45	12	NR	+
3. Burkhoff	132	1	61	NR	100	44	12	22	NR
4. Burns	932	21	62	77	75	49	10	NR	+
5. Cooley	21	1	63	57	NR	48	10	24	+
6. De Carlo	34	1	67	88	59	47	3	15	+
7. Dowling	85	14	63	72	100	48	12	22	+
8. Guleserian	34	1	61	NR	NR	NR	9	NR	ND
9. Hattler	76/91	13	64/61	75/79	100/100	NR	16/3	26/14	NR
10. Horvath	200	8	63	78	100	45	9	18	+
11. Horvath f/u	78	13	NR	NR	NR	NR	N/A	42 (5 year)	+
12. Landolfo	34	1	61	76	100	51	6	15	+
13. Lee	15	1	63	80	100	38	7	13	+
14. Muxi	16	1	60		100	57	0	6 (6 months)	+
15. Nagele	60	1	64	57	100	54	12	23	ND
16. Peterson	661	173	62	53	78	46	6	NR	NR
17. Schneider	14	1	65	57	NR	52	0	36 (36 months)	ND
Total	2549								

TMR plus CABG

Table 3. Characteristics of RCT studies of TMR + CABG

Author	N	# centers	Mean age (years)	Quality Score (out of 4)	Previous MI (%)	III/IV (%)	LVEF (%)	30- d mortality (%)	12 m mortality (%)	Long term mortality (%)	Angina
Allen	263	24	64	3	34	NR	51	1.5	5	24% (5 year)	ND

Table 4. Characteristics of Observational studies of TMR + CABG

Author	N	# centers	Mean age (years)	Previous MI (%)	III/IV (%)	LVEF (%)	30-d mortality (%)	12-m mortality (%)	Angina
1. Gregoric	17	1	63	71	76	33	6	6 (6 m)	+
2. Guleserian	47	1	61	NR	NR	NR	4	NR	ND
3. Peterson	2475	173	65	50	58	50	4	NR	NR
4. Schneider	27	1	64	77	NR	51	0	11 (36 m)	+
5. Stamou	166	1	63	64	90	NR	8	15	+
6. Wehberg	36	1	63	NR	100	52	0	NR	ND
Total	2768								

Table 5. Mortality in studies that compare TMR as sole therapy vs. TMR + CABG

Author	TMR (%)	TMR + CABG (%)
1. Guleserian (30 day)	9	4
2. Peterson (30 day)	6	4
3. Wehberg (30 day)	2	0
4. Schneider (36 month)	36	11
5. Burns (30 day)	10 (no differentiated mortality data)	

PMR

Table 6. Characteristics of RCT studies of PMR

Author	N	# centers	Mean age (years)	Quality Score (out of 4)	Previous MI (%)	III/IV (%)	LVEF (%)	30- d mortality (%)	12 m mortality (%)	Angina	Other
1. DIRECT	196	Multi	63	N/A	NR	NR	NR	4/8	11/14	ND	Exercise, MACE
2. Gray	73	1	61	3	72	100	48	0	3	+	Exercise, QoL
3. Oesterle	221	13	62	3	65	100	NR	NR	7	+	Exercise, QoL
4. Salem	82	2	66	5	63	100	64	0	0	+	QoL
5. Stone	141	17	65	4	65	100	52	0	9	ND	NR
6. Whitlow	330	20	63	3	67	100	47	NR	8	+	Events, Exercise, QoL
Total	843										

Table 7. Characteristics of Observational studies of PMR

	N	# centers	Mean age (years)	30-d mortality (%)	6-m mortality (%)	Angina	Previous MI (%)	Class III/IV (%)	LVEF (%)
1. Kaul	35	1	62	0	0	+	60	100	38
2. Kornowski	77	3	61	0	0	+	68	NR	48
Total	112								

+: Study showed significant improvement in angina

ND: Study did not show significant improvement in angina

NR: Not reported

Appendix 8.3 Quality Score Description

RCT Quality Score

The Jadad et al. (1996) instrument for assessing the quality of randomized clinical trials was used as the basis for developing the RCT quality score used in this report.

1. Randomized – was the study described as randomized (this includes the use of words such as randomly, random and randomization)
   - To receive a "1" the randomization must be described and appropriate, as described in Jadad, 1996
2. Blinded – was the study described as double blind
   - To receive a "1" the blinding must be described and appropriate, as described in Jadad, 1996
3. Withdrawals/ dropouts described – was there a description of withdrawals and dropouts
   - To receive a "1" the withdrawls/dropouts must be described
4. Targeting strategy defined – did the authors adequately describe the section of myocardium targeted for revascularization (where the channels were placed and why)
   - To receive a "1" the targeting strategy must be adequately described

Observational Study Quality Score

The Sackett (1996) prognosis worksheet was used to develop the summative quality score for observational studies.

1. Patients identified at common point – Was a defined, representative sample of patients assembled at a common point in the course of their disease (at the point prior treatment failed).
   Examples of situations warranting a score of 0 for this quality point:
   - a mix of patients who failed and who have not failed;
   - inclusion of patients who fit a wide variety of definitions of failure
2. Sufficient follow-up – Was patient follow-up sufficiently long and complete? (≥ 30 days)
3. Blinded outcome assessment – Were objective outcome criteria applied in a "blind" fashion? (Angina assessed by someone other than the surgical team OR objective measures used – e.g. thallium stress test)
4. Measurement and adjustment for confounders – If subgroups with different prognoses are identified, was there adjustment for important prognostic factors?
5. Targeting strategy defined – did the authors adequately describe the section of myocardium targeted for revascularization (where the channels were placed and why)

Transmyocardial Revascularization – Randomized Controlled Trials

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Aaberge 2000

#490</td>
<td>Geographic Location: Norway

Number of centers:1

Dates of data collection: 1995-98

Technology: TMR alone

Type of laser used: CO2

Number of channels: 47

Consecutive enrollment: Y

Length of follow-up: 1 year

Control: medical therapy</td>
<td>N overall: 100
N int:50
N con:50

N women: 14

Mean age: 62.5

Age range: NR

Race: NR

Angina Class
III: 71
IV: 29</td>
<td>Inclusion Criteria: Refractory angina not candidates for PCI/CABG

Exclusion Criteria: Age>75; LVEF<30 No ischemia; HF; Inability to have tests or surgery

History (n intervention)
Diabetes:11

Hyperlipidemia:38

Hypertension:14

Family History: NR
Prior MI: 35

Pre-operative unstable angina: NR
Prior PCI/ CABG: 45
P.V.D:15

Exam (intervention)
Ejection Fraction: 49%

LVEF < 30%: NR

Objective evidence of ischemia:
DSE or Tetrofosmin</td>
<td>Symptom Status

Intervention
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class</th><th colspan="2">2+ Angina Class improvement</th><th colspan="2">Exercise time (sec)</th><th>Hospital</th></tr>
<tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>N</th></tr>
<tr><td>1</td><td>47/49</td><td>96</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>46/49</td><td>94</td><td>2.3*</td><td>-</td><td>14</td><td>29*</td><td>538</td><td>148</td><td>-</td></tr>
<tr><td>12</td><td>43/49</td><td>88</td><td>2.0*</td><td>-</td><td>19</td><td>39*</td><td>550</td><td>152</td><td>40</td></tr>
</table>
Control
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class</th><th colspan="2">2+ Angina Class improvement</th><th colspan="2">Exercise time (sec)</th><th>Hospital</th></tr>
<tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>N</th></tr>
<tr><td>3</td><td>48/50</td><td>96</td><td>3.1</td><td>-</td><td>0</td><td>0</td><td>570</td><td>176</td><td>-</td></tr>
<tr><td>12</td><td>46/50</td><td>92</td><td>3.1</td><td>-</td><td>0</td><td>0</td><td>560</td><td>184</td><td>45</td></tr>
</table>
*p<0.01 comparing relative changes between groups</td>
<td>Randomization described and appropriate: 1

Double- blinding described and appropriate: 0

Withdrawals/ dropouts described: 1

Targeting strategy defined: 0

Total: 2

Notes:
1 patient randomized to TMR underwent concurrent LIMA bypass and was excluded from f/u</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>scan

Severity of disease:
LM 12
3-v: 44
2-v: 6</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Aaberge 2002

#80</td><td>Geographic Location: Norway

Number of centers: 1

Dates of data collection: 2000-2001 (original operations 1995-99)

Technology: TMR alone

Type of laser used: CO2

Number of channels: 48 +/-7

Consecutive enrollment: Yes

Length of follow-up: 32-60 months</td><td>N overall: 99
N int: 49
N con: 50

N women: 14

Mean age: 62.5

Age range: NR

Race: NR

Angina Class*
III: 71
IV: 29
*taken from original article</td><td>Inclusion Criteria: Class III/IV angina refractory to medical rx not amenable to PCI/CABG

Exclusion Criteria: Age>75; LVEF<30%; No reversible ischemia; Overt HF; Inability to undergo study tests or surgery

History (n intervention)
Diabetes: 11

Hyperlipidemia: 37

Hypertension: 14

Family History: NR

Prior MI: 34

Pre-operative unstable angina:NR

Prior PCI/ CABG: 44</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class</th><th>Hospital during f/u</th><th colspan="2">2+ Angina Class improvement</th><th colspan="2">1+ Angina Class improvement</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>N</th><th>N</th><th>%</th><th>N</th><th>%</th></tr><tr><td>32-60</td><td>38/49</td><td>78</td><td>IV:18%
III:13%
II:39%
I:21%</td><td>-</td><td>138</td><td>9</td><td>24*</td><td>23</td><td>61**</td></tr></table>
Control
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class</th><th>Hospital during f/u</th><th colspan="2">2+ Angina Class improvement</th><th colspan="2">1+ Angina Class improvement</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>N</th><th>N</th><th>%</th><th>N</th><th>%</th></tr><tr><td>32-60</td><td>37/50</td><td>76</td><td>IV:27%
III:78%
II:16%
I: 0%</td><td>-</td><td>181</td><td>1</td><td>3</td><td>9</td><td>24</td></tr></table>
*p=0.001
**p=0.010</td><td>Randomization described and appropriate: 1

Double-blinding described and appropriate: 0

Withdrawals/ drop-outs described: 1

Targeting strategy defined: 0

Total: 2

Notes:
This is f/u to Aaberge study #490</td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td>Control:
medical
therapy</td><td></td><td>P.V.D:
15

Exam (intervention)
Ejection Fraction
(mean): 49%

LVEF < 30%: NR

Objective evidence
of ischemia:
DSE or SPECT

Severity of disease:
3-v dz: 43
LM dz: 12</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Allen
1999

#530</td><td>Geographic
Location:
US

Number of
centers: 18

Dates of data
collection:
1996-98

Technology:
TMR alone

Type of laser
used:
Holmium

Number of
channels: 39+/-
11

Consecutive
enrollment:</td><td>N overall:
275
N int: 132
N con:
143

N women:
68

Mean age:
60

Age range:
NR

Race:
NR

Angina
Class
III: 0
IV: 275</td><td>Inclusion Criteria:
Medically refractory
class IV angina not
amenable to
PCI/CABG
Reversible ischemia
within distal 2/3 of
LV
LVEF> 25%

Exclusion Criteria:
Contraindication for
general anesthesia
Severe COPD
(FEV1< 55%)
Need for IV
antianginals
Inability to undergo
thallium
NQWMI within 2
wks
QWMI within 3 wks
Long-term
anticoagulation</td><td>Symptom Status

Intervention
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Improvement in Angina 2+ classes</th><th colspan="2">Freedom from treatment failure</th><th>Ischemia on thallium</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>%</th><th>N</th><th>%</th><th>% change from baseline</th></tr>
<tr><td>1</td><td>125/132</td><td>95</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>-</td><td>-</td><td>95/115</td><td>83*</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>6</td><td>-</td><td>-</td><td>84/98</td><td>86*</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>12</td><td>111/132</td><td>84</td><td>58/76</td><td>76*</td><td>96/132</td><td>73*</td><td>-0.9</td></tr>
</table></td><td>Randomization
described and
appropriate: 1

Double-blinding
described and
appropriate: 0

Withdrawals/ drop-
outs described: 0

Targeting strategy
defined: 1

Total: 2

Notes:
Control group
divided into 97 who
received medicine
only plus 46 that
were “treatment
failures” and</td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td>Yes

Length of follow-up: 1 year

Control: medical therapy</td><td></td><td>Mural thrombus
Severe arrhythmias
Decompensated CHF

History (n intervention)
Diabetes: 61
Hyperlipidemia: 104
Hypertension: 92
Family History: 66
Prior MI: 84
Pre-operative unstable angina: NR
Prior PCI/CABG: 121

P.V.D:NR

Exam (intervention)
Ejection Fraction/ LVEF < 30%:
Mean LVEF 47%

Objective evidence of ischemia: Dipyridamole-thallium

Severity of disease: NR</td><td>Control
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Improvement in Angina 2+ classes</th><th colspan="2">Freedom from treatment failure</th><th>Ischemia on thallium</th></tr><tr><th>N</th><th>%</th><th>N</th><th>%</th><th>N</th><th>%</th><th>% change from baseline</th></tr><tr><td>1</td><td>95/97</td><td>98</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>3</td><td>-</td><td>-</td><td>13/98</td><td>13</td><td>-</td><td>-</td><td>-</td></tr><tr><td>6</td><td>-</td><td>-</td><td>15/74</td><td>20</td><td>-</td><td>-</td><td>-</td></tr><tr><td>12</td><td>127/143**</td><td>89</td><td>16/50</td><td>32</td><td>67/143</td><td>47</td><td>-0.6</td></tr></table>
*p<0.001 relative to control
**when crossover group excluded: 85/97 (88%)

“Crossover” patients were those initially randomly assigned to medical therapy (control) who met criteria for treatment failure and underwent TMR as part of a separate protocol. Results were not significantly different from the randomly assigned TMR intervention group.

Crossover
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class</th><th colspan="2">Improvement in Angina 2+ classes</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>N</th><th>%</th></tr><tr><td>1</td><td>42/46</td><td>91</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>3</td><td>-</td><td>-</td><td>-</td><td>-</td><td>20/23</td><td>87</td></tr><tr><td>6</td><td>-</td><td>-</td><td>-</td><td>-</td><td>27/33</td><td>82</td></tr><tr><td>12</td><td>42/46</td><td>91</td><td>-</td><td>-</td><td>29/37</td><td>78</td></tr></table></td><td>crossed-over into TMR</td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Allen 2004

#1660</td>
<td>Geographic Location:
US
Number of centers: 9

Dates of data collection:
1996-1998

Technology:
TMR alone

Type of laser used:
Holmium

Number of channels: 39+/-11

Consecutive enrollment:
Yes

Length of follow-up: 5 years

Control:
medical therapy</td>
<td>N overall:
212
N int: 100
N con:
112

N women:
52

Mean age:
60

Age range:
NR

Race:
NR

Angina Class
III: 0
IV: 212</td>
<td>Inclusion Criteria:
Medically refractory class IV angina not amenable to PCI/CABG
Reversible ischemia within distal 2/3 of LV
LVEF> 25%

Exclusion Criteria:
Contraindication for general anesthesia
Severe COPD (FEV1< 55%)
Need for IV antianginals
Inability to undergo thallium
NQWMI within 2 wks
QWMI within 3 wks
Long-term anticoagulation
Mural thrombus
Severe arrhythmias
Decompensated CHF

History (n intervention)
Diabetes:
43
Hyperlipidemia:
78
Hypertension:
70
Family History:
63
Prior MI:</td>
<td>Symptom Status

Intervention
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class</th><th colspan="2">Improvement in Angina 2+ classes</th><th colspan="2">Angina-free</th></tr>
<tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>N</th><th>%</th><th>N</th><th>%</th></tr>
<tr><td>1</td><td>-</td><td>97</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>-</td><td>-</td><td>1.4*</td><td>1.3</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>6</td><td>-</td><td>-</td><td>1.3*</td><td>1.2</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>12</td><td>-</td><td>-</td><td>1.5*</td><td>1.4</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>60</td><td>-</td><td>65</td><td>1.2*</td><td>1.1</td><td>42/48</td><td>88**</td><td>16/48</td><td>33***</td></tr>
</table>
Control
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Improvement in Angina 2+ classes</th><th colspan="2">Angina-free</th></tr>
<tr><th>N</th><th>N</th><th>N</th><th>SD</th><th>N</th><th>%</th></tr>
<tr><td>60</td><td>-</td><td>52</td><td>16/36</td><td>44</td><td>4/36</td><td>11</td></tr>
</table>
When crossover group is excluded:
Survival at 60 months = 53%
Improvement in Angina 2+ classes = 10/27 (37%)

*p<0.0001 compared to control
**p<0.001 compared to control
***p=0.02

Crossover (29 of 112 med rx pts had TMR)
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Improvement in Angina 2+ classes</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>%</th></tr>
<tr><td>1</td><td>-</td><td>93</td><td>-</td><td>-</td></tr>
<tr><td>60</td><td>-</td><td>48</td><td>6/9</td><td>67</td></tr>
</table>
</td>
<td>Randomization described and appropriate: 1

Double-blinding described and appropriate: 0

Withdrawals/ drop-outs described: 0

Targeting strategy defined: 1

Total: 2

Notes:
This is 5-yr f/u paper with subset of patients from Allen study #530</td>
</tr>
</table>

Comment [PC1]:

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>84
Pre-operative unstable angina: NR
Prior PCI/CABG: 92

P.V.D:NR

Exam (intervention)
Ejection Fraction (mean): 47%

LVEF < 30%: NR

Objective evidence of ischemia: Dipyridamole-thallium

Severity of disease: NR</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Burkhoff 1999a

#1480</td><td>Geographic Location: US

Number of centers: 16

Dates of data collection: NR

Technology: TMR alone

Type of laser used: Holmium</td><td>N overall: 182
N int: 92
N con: 90

N women: 17 (it appears that the numbers for M/F are reversed in table 1)

Mean age: 64

Age range: 36-78</td><td>Inclusion Criteria:
Refractory Class III/IV angina
LVEF >=30%
Reversible ischemia by thallium

Exclusion Criteria:
Patients without1 “protected” region
USA
Substantial change in angina
Change in angina meds <21 d
MI < 3 mo
Severe CHF
Cardiac transplant
Poor surgical</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th>Change in Exercise time (sec)</th><th colspan="2">2+ angina class improvement</th><th>reversible defects</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>N</th><th>%</th><th>%</th></tr><tr><td>1</td><td>91/92</td><td>99</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>12</td><td>87/92</td><td>95</td><td>+65*</td><td>47/77</td><td>61</td><td>11.5</td></tr></table>
Control
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th>Change in Exercise time (sec)</th><th colspan="2">2+ angina class improvement</th><th>reversible defects</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>N</th><th>%</th><th>%</th></tr><tr><td>1</td><td>90/90</td><td>100</td><td>-</td><td>-</td><td>-</td><td>-</td></tr></table></td><td>Randomization described and appropriate: 1

Double-blinding described and appropriate: 0

Withdrawals/ drop-outs described: 1

Targeting strategy defined: 1

Total: 3

Notes:</td></tr>
</table>

Study	Characteristics	No. of Patients	Patient Population	Outcomes	Quality Score
	Number of channels: 18 (9-42) Consecutive enrollment: Yes Length of follow-up: 1 year Control: medical therapy	Race: NR Angina Class III: 70 IV: 112	candidates History (n intervention) Diabetes: 33 Hyperlipidemia: 71 Hypertension: 68 Family History: 66 Prior MI: 64 Pre-operative unstable angina: 0 Prior PCI/ CABG: 43 P.V.D: NR Exam (intervention) Ejection Fraction (mean): 50% LVEF < 30%: NR Objective evidence of ischemia: Dipyridamole-thallium Severity of disease: NR	12 | 81/90 | 90 | -46 | 8/73 | 11 | 12 *p<0.0001	

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Frazier 1999

#520</td>
<td>Geographic Location:
US

Number of centers:
12

Dates of data collection:
1995-98

Technology:
TMR alone

Type of laser used:
CO2

Number of channels:
36 ± 13

Consecutive enrollment:
Yes

Length of follow-up:
1 tear

Control:
medical therapy</td>
<td>N overall:
192
N int: 91
N con: 101

N women:
40

Mean age:
61 years

Age range:
NR

Race: NR

Angina Class
III: 76
IV: 126</td>
<td>Inclusion Criteria:
Refractory Class III/IV angina not amenable to PCI/CABG
Reversible ischemia of LV free wall

Exclusion Criteria:
LVEF<20%
Major concurrent illness

History (n intervention)
Diabetes: 36

Hyperlipidemia:52

Hypertension:59

Family History:NR

Prior MI: 75

Pre-operative unstable angina: 7

Prior PCI: 43
CABG: 84

P.V.D: NR

Exam (intervention)
Ejection Fraction (mean): 50%

LVEF < 30%: NR</td>
<td>Symptom Status

Intervention
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">2+ angina class improvement</th><th colspan="3">Change in perfusion</th><th>Hospital-ization</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>%</th><th>N</th><th>%</th><th>p</th><th>%</th></tr>
<tr><td>1</td><td>88/91</td><td>97</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>85/91</td><td>93</td><td>52/78</td><td>67*</td><td>50</td><td>+22</td><td>0.001</td><td>-</td></tr>
<tr><td>6</td><td>81/91</td><td>89</td><td>45/67</td><td>67*</td><td>47</td><td>+14</td><td>0.02</td><td>-</td></tr>
<tr><td>12</td><td>78/91</td><td>85</td><td>44/61</td><td>72*</td><td>38</td><td>+20</td><td>0.002</td><td>2*</td></tr>
</table>
Control
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">2+ angina class improvement</th><th colspan="2">Change in perfusion</th><th>Hospital-ization</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>%</th><th>N</th><th>%</th><th>%</th></tr>
<tr><td>1</td><td>38/41</td><td>93</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>38/41</td><td>93</td><td>1/24</td><td>6</td><td>38</td><td>-13</td><td>-</td></tr>
<tr><td>6</td><td>37/41</td><td>90</td><td>1/24</td><td>6</td><td>35</td><td>-12</td><td>-</td></tr>
<tr><td>12</td><td>34/41</td><td>79</td><td>3/20</td><td>13</td><td>13</td><td>-27</td><td>69</td></tr>
</table>
*p<0.001 for comparison with control

Crossover (60 of med rx patients crossed-over to TMR)
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">2+ angina class improvement</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>%</th></tr>
<tr><td>1</td><td>51/60</td><td>85</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>51/60</td><td>85</td><td>14/53</td><td>26</td></tr>
<tr><td>6</td><td>50/60</td><td>83</td><td>17/43</td><td>40</td></tr>
<tr><td>12</td><td>45/60</td><td>75</td><td>20/34</td><td>59</td></tr>
</table>
</td>
<td>Randomization described and appropriate: 1

Double-blinding described and appropriate: 0

Withdrawals/ drop-outs described: 0

Targeting strategy defined: 0

Total:
1

Notes:
Angina improvement for med rx group + crossovers was 20%, 27% and 43% at 3,6, and 12 months.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Objective evidence of ischemia: Thallium

Severity of disease: 3 v dz: 100%</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Huikes-hoven 2003

#1760</td><td>Geographic Location: Netherlands

Number of centers: 1

Dates of data collection:

Technology: TMR alone

Type of laser used: Excimer

Number of channels: 46 +/- 10

Consecutive enrollment: Yes

Length of follow-up: 12 months

Control: medical therapy</td><td>N overall: 30
N int: 15
N con: 15

N women: 3

Mean age: 60.4

Age range: NR

Race: NR

Angina Class
III: NR
IV: NR
Mean: 3.8</td><td>Inclusion Criteria: Refractory Class III/IV angina Reversible ischemia

Exclusion Criteria: NR

History (n intervention)
Diabetes: NR

Hyperlipidemia: NR

Hypertension: NR

Family History: NR

Prior MI: NR

Pre-operative unstable angina: NR

Prior PCI: 7
CABG:15

P.V.D: NR</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">EuroQOL mobility</th><th colspan="2">EuroQOL usual activity</th><th colspan="2">EuroQOL pain</th></tr><tr><th>N</th><th>%</th><th>score</th><th>SD</th><th>score</th><th>SD</th><th>score</th><th>SD</th></tr><tr><td>1</td><td>15/15</td><td>100</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>12</td><td>14/15</td><td>93</td><td>2.3</td><td>0.5</td><td>2.5*</td><td>0.5</td><td>2.2</td><td>0.6</td></tr></table>
Control
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">EuroQOL mobility</th><th colspan="2">EuroQOL usual activity</th><th colspan="2">EuroQOL pain</th></tr><tr><th>N</th><th>%</th><th>score</th><th>SD</th><th>score</th><th>SD</th><th>score</th><th>SD</th></tr><tr><td>1</td><td>15/15</td><td>100</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>12</td><td>15/15</td><td>100</td><td>2.3</td><td>0.5</td><td>1.7</td><td>0.6</td><td>1.8</td><td>0.7</td></tr></table>
*p<0.01</td><td>Randomization described and appropriate:1

Double-blinding described and appropriate: 0

Withdrawls/ drop-outs described: 0

Targeting strategy defined: 0

Total: 1

Notes:</td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Exam (intervention)
Ejection Fraction:
Mean 55%

Objective evidence of ischemia: NR

Severity of disease:
NR</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Jones
1999

#610</td><td>Geographic Location:
US
Number of centers:
1
Dates of data collection:
1996-97

Technology:
TMR alone

Type of laser used:
Holmium

Number of channels: NR

Consecutive enrollment:
Yes

Length of follow-up:
1 year</td><td>N overall:
86
N int:43
N con:43

N women:
0

Mean age:
62

Age range:
NR

Race:
NR

Angina Class
III: NR
IV: NR</td><td>Inclusion Criteria:
Class III/IV angina not amenable to PCI/CABG
Ischemia by thallium
1 area with adequate perfusion by cath

Exclusion Criteria:
Acs requiring hospitalization < 21 days
Revasc or MI < 3 months
EF< 30%
COPD if felt to preclude exercise testing
LM > 70% without bypass to LAD or LCX
CHF

History (n intervention)
Diabetes:
NR</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">angina class improvement</th><th>Exer time (sec)</th><th colspan="2">Sx improvement</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>Mean</th><th>N</th><th>%</th></tr><tr><td>1</td><td>42/43</td><td>98</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>3</td><td>-</td><td>-</td><td>-</td><td>-</td><td>481**</td><td>36/41</td><td>88</td></tr><tr><td>6</td><td>-</td><td>-</td><td>-</td><td>-</td><td>514***</td><td>-</td><td>-</td></tr><tr><td>12</td><td>38/43</td><td>88</td><td>1.71*</td><td>0.2</td><td>490***</td><td>34/41</td><td>83</td></tr></table>
Control
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">angina class improvement</th><th>Exer time (sec)</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>Mean</th></tr><tr><td>1</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>3</td><td>-</td><td>-</td><td>-</td><td>-</td><td>334</td></tr><tr><td>6</td><td>-</td><td>-</td><td>-</td><td>-</td><td>316</td></tr><tr><td>12</td><td>38/43</td><td>88</td><td>3.77</td><td>0.07</td><td>294</td></tr></table>
*p<0.0001
**p=0.0002
***p=0.0001</td><td>Randomization described and appropriate: 1

Double-blinding described and appropriate: 0

Withdrawals/ drop-outs described: 0

Targeting strategy defined: 1

Total: 2

Notes:
No 30 day mortality in control arm reported—consider exclusion</td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Hyperlipidemia:
NR
Hypertension:
27
Family History:
NR
Prior MI:
31
Pre-operative unstable angina:
0
Prior PCI/ CABG:
41
P.V.D: NR

Exam (intervention)
Ejection Fraction (mean): 46.3%

LVEF < 30%: NR

Objective evidence of ischemia:
Dipyridamole thallium

Severity of disease:
Avg numdz v 2.5</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Schofield 1999

#1490</td><td>Geographic Location: UK

Number of centers:1

Dates of data collection:
1993-98

Technology:
TMR alone</td><td>N overall:
188
N int:94
N con:94

N women:
19

Mean age:
60

Age range:</td><td>Inclusion Criteria:
Reversible ischemia

Exclusion Criteria:
Unable to exercise
LVEF < 30%
Suitable for PCI/CABG
IV therapy for angina
Life expectancy <12 months from non-</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th>Exer time difference (sec)</th><th colspan="2">2+ angina class improvement</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>N</th><th>%</th></tr><tr><td>1</td><td>89</td><td>95</td><td>-</td><td>-</td><td>-</td></tr><tr><td>3</td><td>-</td><td>-</td><td>+43</td><td>23*</td><td>34</td></tr><tr><td>6</td><td>-</td><td>-</td><td>+36</td><td>15*</td><td>22</td></tr><tr><td>12</td><td>-</td><td>89</td><td>+40</td><td>18*</td><td>25</td></tr></table></td><td>Randomization described and appropriate: 1

Double-blinding described and appropriate: 0

Withdrawals/ drop-outs described: 1

Targeting strategy</td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr>
<td></td>
<td>Type of laser used:
CO2

Number of channels:
Median 30 (6-75)

Consecutive enrollment:
Yes

Length of follow-up: 3 years

Control:
medical management</td>
<td>NR

Race:
NR

Angina Class
III: 138
IV: 50</td>
<td>cardiac reason

History (n intervention)
Insulin dep Diabetes:
18
Hyperlipidemia:
NR
Hypertension:
NR
Family History:
NR
Prior MI:
69
Pre-operative unstable angina:
NR
Prior PCI: 27
CABG: 89

P.V.D:NR

Exam (intervention)
Ejection Fraction (mean): 48%

LVEF < 30%: NR

Objective evidence of ischemia:
Sestamibi

Severity of disease:
NR</td>
<td>Control
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">2+ angina class improvement</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>%</th></tr>
<tr><td>1</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>-</td><td>-</td><td>2</td><td>3</td></tr>
<tr><td>6</td><td>-</td><td>-</td><td>3</td><td>4</td></tr>
<tr><td>12</td><td>-</td><td>96</td><td>3</td><td>4</td></tr>
</table>
*p<0.001</td>
<td>defined: 0

Total: 2

Notes:</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr>
<td>Agarwal 1999

#700</td>
<td>Geographic Location: Madras, India

Number of centers: 1

Dates of data collection: 12/94-9//97

Technology: TMR alone

Type of laser used: 800-W CO_2 laser

Number of channels: 23±8

Consecutive enrollment: Yes

Length of follow-up: 12 months</td>
<td>N overall: 102

N women: 8

Mean age: 56.7± 9.2 years

Age range: 30-79 years

Race: NR

Angina Class (n)
II: 47
III: 44
IV: 11</td>
<td>Inclusion Criteria: Severe angina refractory to maximal medical therapy not amenable to conventional PTCA and CABG

Exclusion Criteria: LVEF < 30%; No evidence of reversible ischemia

History (n)
Diabetes: 50

Hyperlipidemia: 43

Hypertension: 51

Family History: NR

Prior MI: 33

Pre-operative unstable angina: 9

Prior PCI/ CABG: 13

P.V.D: NR

Exam
Ejection Fraction: 44.7%±10.5%

Objective evidence of ischemia: Stress thallium</td>
<td>Symptom Status

Intervention
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th colspan="2">Angina Class</th><th colspan="2">TMT duration (min)</th><th colspan="2">LVEF</th></tr>
<tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>Mean</th><th>SD</th><th>Mean</th><th>SD</th></tr>
<tr><td>1</td><td>15/102</td><td>14.7</td><td>0.7</td><td>1.1</td><td>6.5</td><td>3.4</td><td>42.2</td><td>11.7</td></tr>
<tr><td>3</td><td>-</td><td>-</td><td>0.7</td><td>1.0</td><td>6.5</td><td>3.4</td><td>45.6</td><td>18.0</td></tr>
<tr><td>6</td><td>-</td><td>-</td><td>0.8</td><td>1.1</td><td>8.0</td><td>3.7</td><td>46.0</td><td>11.6</td></tr>
<tr><td>12</td><td>17/102</td><td>16.7</td><td>0.8</td><td>0.9</td><td>9.7</td><td>4.0</td><td>42.0</td><td>11.7</td></tr>
</table></td>
<td>Patients identified at common point: 0

Sufficient follow-up: 0

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 0

Notes:</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Severity of disease: LM 13</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Allen 1998

#780</td><td>Geographic Location: Louisville, KY

Number of centers: 2

Dates of data collection: 1/96-1/97

Technology: TMR alone

Type of laser used: Holmium YAG laser

Number of channels: 45±11

Consecutive enrollment: Yes

Length of follow-up: 12 months</td><td>N overall: 42

N women: 14

Mean age: 62±11 years

Age range: 38-79 years

Race: NR

Angina Class
III: 3
IV: 39</td><td>Inclusion Criteria: Refractory angina not amenable to PTCA/CABG; Stable class IV or unstable angina unable to be weaned fron intravenous antianginals; CAD not amenable to PTCA/ CABG; evidence of ischemic myocardium; LVEF>25%

Exclusion Criteria: Intolerance to anesthesia; Uncompensated heart failure; severe arrhythmia; chronic anticoagulation; hemorrhagic propensity

History (n)
Diabetes: 22

Hyperlipidemia: 31

Hypertension: 31

Family History: NR

Prior MI: 29</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th colspan="2">Angina Class</th><th colspan="2">Dropped ≥2 angina classes</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>N</th><th>%</th></tr><tr><td>1</td><td>5/42</td><td>12</td><td>-</td><td>-</td><td>-</td><td></td></tr><tr><td>3</td><td>-</td><td>-</td><td>1.5</td><td>0.1</td><td>29</td><td>88</td></tr><tr><td>6</td><td>-</td><td>-</td><td>1.1</td><td>0.1</td><td>18</td><td>80</td></tr></table></td><td>Patients identified at common point: 1

Sufficient follow-up: 0

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 1

Notes:</td></tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Pre-operative unstable angina: 19

Prior PCI/ CABG: 19/31

P.V.D: NR

Exam
Ejection Fraction: 45%±11% (30%-84%)

Objective evidence of ischemia: NR

Severity of disease: NR</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Burkhoff 1999b

#650</td><td>Geographic Location: Louisville, KY

Number of centers: 1

Dates of data collection: 2/94-10/96

Technology: TMR alone

Type of laser used: CO_2

Number of channels: NR</td><td>N overall: 132

N women: 23

Mean age: 61.1±11.3 years

Age range: 38-84 years

Race: NR

Angina Class
III: 7
IV: 125</td><td>Inclusion Criteria: Medically refractory angina class III or IV

Exclusion Criteria: NR

History (n)
Diabetes: NR

Hyperlipidemia: NR

Hypertension: NR

Family History: NR

Prior MI: NR</td><td>Symptom Status

Intervention
<table><tr><th>Month</th><th colspan="2">Deaths</th></tr><tr><th></th><th>N</th><th>%</th></tr><tr><td>1</td><td>16/132</td><td>12.1</td></tr><tr><td>12</td><td>29/132</td><td>22</td></tr></table></td><td>Patients identified at common point: 1

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 2</td></tr>
</table>

Study	Design	No. of Patients	Patient Population	Outcomes	Quality Score
	Consecutive enrollment: NR Length of follow-up: NR		Pre-operative unstable angina: 63 Prior PCI/ CABG: 111 P.V.D: NR Exam Ejection Fraction: 44%±12% (15%-68%) Objective evidence of ischemia: NR Severity of disease: NR		Notes:
Burns 1999 #1590	Geographic Location: International Number of centers: 21 Dates of data collection: 11/93-4/97 Technology: TMR alone; TMR with CABG Type of laser used: CO_2 Number of channels: 28.6±12.2	N overall: 932 N women: 148 Mean age: 62±8.7 years Age range: 32-84 years Race: NR Angina Class III and IV: n=699	Inclusion Criteria: Availability of patient characteristics, risk factors and cardiac history, operative details, combined procedures and in-hospital complications Exclusion Criteria: NR History (n) Diabetes: 212 Hyperlipidemia: NR Hypertension: 339 Family History: NR Prior MI: 713	*Symptom Status* • Includes TMR and TMR/CABG • High variation across centers in reporting information/ follow-up • In-hospital mortality: 90	Patients identified at common point: 1 Sufficient follow-up: 0 Blinded outcome assessment: 0 Measurement and adjustment for confounders: 0 Targeting strategy defined: 0 Total: 1 Notes:

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td>Consecutive enrollment: NR

Length of follow-up: 12 months</td><td></td><td>Pre-operative unstable angina: 437

Prior PCI/ CABG: 209/500

P.V.D: 193

Exam
Ejection Fraction: 49%±14.9%

LVEF<30%: 10%

Objective evidence of ischemia: NR

Severity of disease: NR</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Cooley 1996

#1650</td><td>Geographic Location: Houston, TX

Number of centers: 1

Dates of data collection: NR

Technology: TMR alone

Type of laser used:
CO_2

Number of channels: 36+/-5</td><td>N overall: 21

N women: 3

Mean age: 63±10 years

Age range: NR

Race: NR

Angina Class
III: NR
IV: NR</td><td>Inclusion Criteria: PET confirmed perfusion defects in left ventricular free wall

Exclusion Criteria: NR

History (n)
Diabetes: 3

Hyperlipidemia: NR

Hypertension: NR

Family History: NR

Prior MI: 12</td><td>Symptom Status

Intervention
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class</th><th colspan="2">TTM (min)</th><th colspan="2">LVEF (%)</th></tr>
<tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>Mean</th><th>SD</th><th>Mean</th><th>SD</th></tr>
<tr><td>1</td><td>19/21</td><td>90%</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>19/21</td><td>90%</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>6</td><td>16/21</td><td>76%</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>12</td><td>16/21</td><td>76</td><td>1.8</td><td>0.6</td><td>10.0</td><td>3.8</td><td>50</td><td>8</td></tr>
</table></td><td>Patients identified at common point: 1

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 1</td></tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td>Consecutive enrollment: Yes

Length of follow-up: 12 months</td><td></td><td>Pre-operative unstable angina: 4

Prior PCI/ CABG: 20

P.V.D: NR

Exam
Ejection Fraction: 48%±10%

LVEF < 35%: n=7

Objective evidence of ischemia: ^{201}Ti-SPECT

Severity of disease: CCS: 3.7±0.4</td><td></td><td>Notes:
Additional data taken from Frazier Circ 192(1) II: 58-65</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>De Carlo 2000

#1570</td><td>Geographic Location: Pisa, Italy

Number of centers: 1

Dates of data collection: 11/95-6/99

Technology: TMR alone

Type of laser used: Holmium: YAG

Number of channels: 36±9</td><td>N overall: 34

N women: 8

Mean age: 67±7 years

Age range: 46-79 years

Race: NR

Angina Class III and IV: 20</td><td>Inclusion Criteria: CCS III/IV refractory to maximal medical treatment; not suitable for PTCA/ CABG; LVEF>30%; Ischemia and viability shown on Ti-SPECT

Exclusion Criteria: NR

History (n)
Diabetes: 14

Hyperlipidemia: 21

Hypertension: 19

Family History: NR</td><td>Symptom Status

Intervention
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Dropped ≥2 angina classes</th><th colspan="2">Angina Class</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>%</th><th>Mean</th><th>SD</th></tr>
<tr><td>1</td><td>33/34</td><td>97</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>12</td><td>29/34</td><td>85</td><td>10/23</td><td>43.5</td><td>1.8</td><td>1.8</td></tr>
<tr><td>36</td><td>25/34</td><td>74</td><td>7/23</td><td>30</td><td>-</td><td>-</td></tr>
</table></td><td>Patients identified at common point: 1

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 1

Targeting strategy defined: 0

Total: 3</td></tr>
</table>

Study	Design	No. of Patients	Patient Population	Outcomes	Quality Score
	Consecutive enrollment: Yes Length of follow-up: 35±10 months		Prior MI: 30 Pre-operative unstable angina: 14 Prior PCI/ CABG: 13/27 P.V.D: NR Exam (n) Ejection Fraction: 47%±9% LVEF < 30%: 0 (excluded) Objective evidence of ischemia: 201Ti-SPECT Severity of disease: CCS: 3.5±0.5		Notes:

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr>
<td>Dowling 1998

#790</td>
<td>Geographic Location: USA

Number of centers: 14

Dates of data collection: 4/96-2/97

Technology: TMR alone

Type of laser used: Holmium laser

Number of channels: 35±11

Consecutive enrollment: Yes

Length of follow-up: 12 months</td>
<td>N overall: 85

N women: 21%

Mean age: 63±10 years

Age range: NR

Race: NR

Angina Class
III: 0
IV: 85</td>
<td>Inclusion Criteria: Refractory angina despite IV therapy; LVEF>25%; Contraindication CABG/PTCA

Exclusion Criteria: Severe COPD; Q wave MI within 3 weeks; Non Q wave MI within 2 weeks; Decompensated heart failure; Life threatening arrhythmias; Bleeding disorder; Mural thrombus

History (n)
Diabetes: 37 (44%)

Hyperlipidemia: 61 (72%)

Hypertension: 67 (79%)

Family History: NR

Prior MI: 61 (72%)

Pre-operative unstable angina: NR

Prior PCI/ CABG: 42 (49%)/ 71 (84%)

P.V.D: NR

Exam
Ejection Fraction: 48%±84%</td>
<td>Symptom Status

Intervention
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th colspan="2">2+ Angina class improvement</th><th colspan="2">Angina Class</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>%</th><th>Mean</th><th>SD</th></tr>
<tr><td>1</td><td>10/85</td><td>12</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>12/85</td><td>15</td><td>63/72</td><td>87.5%</td><td>1.4</td><td>1.1</td></tr>
<tr><td>6</td><td>-</td><td>-</td><td>54/70</td><td>77%</td><td>1.5</td><td>1.1</td></tr>
<tr><td>12</td><td>19/85</td><td>22</td><td>42/57</td><td>75%</td><td>1.6</td><td>1.3</td></tr>
</table>
</td>
<td>Patients identified at common point: 0

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 1

Notes:</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>LVEF < 30%: NR

Objective evidence of ischemia: NR

Severity of disease: NR</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hattler 1999

#1830</td><td>Geographic Location: USA

Number of centers: 13

Dates of data collection: 1995

Technology: TMR alone

Type of laser used: CO_2 laser

Number of channels: UA: 30±9
CA: 33±10

Consecutive enrollment: NR

Length of follow-up: 12 months</td><td>N overall: 76 with unmanageable unstable angina (UA) and 91 with chronic angina (CA)

N women:
UA: 46
CA: 19

Mean age:
UA: 64 years
CA: 61 years

Age range: NR

Race: NR

Angina Class
UA:
IV: 100%
CA:
III: 20%
IV: 80%</td><td>Inclusion Criteria: Chronic angina poorly responsive to medical therapy; a level of angina that would allow thorough preoperative evaluation with radionuclide myocardial perfusion scans; reversible ischemia demonstrated by radionuclide perfusion scans; severe diffuse coronary artery disease; end-stage coronary disease with contraindications to further medical or surgical revascularization or transplantation. Unstable angina patients had to have been admitted to an ICU or CCU with refractory angina for 7 days with three</td><td>Symptom Status

Unmanageable unstable angina
<table><tr><th>Month</th><th colspan="2">Deaths</th><th>Angina III-IV</th><th>Angina I</th></tr><tr><th></th><th>N</th><th>%</th><th>%</th><th>%</th></tr><tr><td>1</td><td>12</td><td>16</td><td>-</td><td>-</td></tr><tr><td>3</td><td>-</td><td>-</td><td>18</td><td>51</td></tr><tr><td>6</td><td>-</td><td>-</td><td>28</td><td>43</td></tr><tr><td>12</td><td>20</td><td>26</td><td>24</td><td>46</td></tr></table>
Chronic angina
<table><tr><th>Month</th><th colspan="2">Deaths</th><th>Angina III-IV</th><th>Angina I</th></tr><tr><th></th><th>N</th><th>%</th><th>%</th><th>%</th></tr><tr><td>1</td><td>3</td><td>3</td><td>-</td><td>-</td></tr><tr><td>3</td><td>-</td><td>-</td><td>24</td><td>47</td></tr><tr><td>6</td><td>-</td><td>-</td><td>26</td><td>49</td></tr><tr><td>12</td><td>10</td><td>14</td><td>33</td><td>50</td></tr></table></td><td>Patients identified at common point: 0

Sufficient follow-up: 0

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 0

Notes: Data on protocol group is follow up of previously reported data (Horvath 1997)</td></tr>
</table>

Study	Design	No. of Patients	Patient Population	Outcomes	Quality Score
			failed attempts at weaning them off intravenous antianginal medications before being taken to the operating room for laser revascularization. Exclusion Criteria: NR History (n) Diabetes: UA: 24; CA: 42 Hyperlipidemia: UA: 39; CA: 56 Hypertension: UA: 37: CA: 58 Family History: NR Prior MI: UA: 57; CA: 72 Pre-operative unstable angina: Prior PCI/ CABG: 66, 83 P.V.D: Exam Ejection Fraction<45%: UA: 38; CA: 32 Objective evidence of ischemia: NR		

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Severity of disease: NR</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Horvath 2001

#1820</td><td>Geographic Location: USA

Number of centers: 8

Dates of data collection: 1993-96

Technology: TMR alone

Type of laser used: CO_2 laser

Number of channels: 20±8

Consecutive enrollment:

Length of follow-up: 5 yrs (max 7.2 yrs)</td><td>N overall: 78 (195 initially)

N women: NR

Mean age: NR

Age range: NR

Race: NR

Angina Class Mean: 3.7±0.4</td><td>Inclusion Criteria: CCS angina class III or IV, be 18 years old, have an ejection fraction of 20%, have evidence of reversible ischemia, and not be candidates for CABG or PCI.

Exclusion Criteria: NR

History (n)
Diabetes: 22

Hyperlipidemia: 53

Hypertension: 51

Family History: NR

Prior MI: NR

Pre-operative unstable angina:51

Prior PCI/ CABG: NR

P.V.D: NR

Exam
Ejection Fraction: NR

Objective evidence of ischemia: NR</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th colspan="2">Angina class</th><th colspan="2">Improvement > 2 class</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>N</th><th>%</th></tr><tr><td>12</td><td>41/195</td><td>21</td><td>1.5</td><td>1.1</td><td>70/195</td><td>35</td></tr><tr><td>60</td><td>82/195</td><td>42</td><td>1.6</td><td>1.1</td><td>53/78</td><td>68</td></tr></table>
Significant improvement in the 5 parameters of the SAQ versus baseline mentioned, although data not shown.</td><td>Patients identified at common point: 0

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 1

Notes: 5 year follow up of previously reported data (Horvath 1997, Frazier 1999).

Patients who died or underwent an additional revascularization were not included in this report.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Severity of disease: NR</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Horvath 1997

#1530</td><td>Geographic Location: USA

Number of centers: 8

Dates of data collection: 8/92-7/95

Technology: TMR alone

Type of laser used: CO2

Number of channels: 30 +/- 12

Consecutive enrollment: Yes

Length of follow-up: 12 months</td><td>N overall: 200

N women: 44

Mean age: 63±10 years

Age range: 35-85 years

Race: NR

Angina Class
III: 40
IV: 160</td><td>Inclusion Criteria: Severe angina refractory to medical therapy; Reversible ischemia; Contraindication of CABG/PTCA

Exclusion Criteria: NR

History (n)
Diabetes: 69

Hyperlipidemia: 133

Hypertension: 131

Family History: NR

Prior MI: 155

Pre-operative unstable angina: 178

Prior PCI/ CABG: 56/164

P.V.D: NR

Exam
Ejection Fraction: 45%±10% (Range 15%-75%)

LVEF < 30%: NR

Objective evidence of ischemia: Stress</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th colspan="2">Dropped ≥2 angina classes</th></tr><tr><th>N</th><th>%</th><th>N</th><th>%</th></tr><tr><td>1</td><td>18</td><td>9</td><td>-</td><td>-</td></tr><tr><td>3</td><td>-</td><td>-</td><td>117/156</td><td>59</td></tr><tr><td>6</td><td>-</td><td>-</td><td>108/143</td><td>54</td></tr><tr><td>12</td><td>35</td><td>18</td><td>70/95</td><td>35</td></tr></table></td><td>Patients identified at common point: 1

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 1

Targeting strategy defined: 0

Total: 3

Notes:</td></tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>scans with thallium or technetium

Severity of disease: NR</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Landolfo 1999

#1600</td><td>Geographic Location: Durham, NC (Duke University)

Number of centers: 1

Dates of data collection: 10/95-8/97

Technology: TMR alone

Type of laser used: CO_2

Number of channels: 22+/-10

Consecutive enrollment: Yes

Length of follow-up: 12 months</td><td>N overall: 34

N women: 14

Mean age: 61±9 years

Age range: 43-75

Race: NR

Angina Class
III:14
IV: 20</td><td>Inclusion Criteria: Severe diffuse CAD not amenable to PTCA/CABG; Evidence of ischemia

Exclusion Criteria: NR

History (n)
Diabetes: 24

Hyperlipidemia: 32

Hypertension: 32

Family History: 21

Prior MI: 26

Pre-operative unstable angina: NR

Prior PCI/ CABG: 31

P.V.D: NR

Exam
Ejection Fraction: 51%±9%

LVEF < 30%:NR

Objective evidence of ischemia: Tl-</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th colspan="2">Dropped ≥2 angina classes</th><th colspan="2">Angina Class</th><th>Hospitalization</th></tr><tr><th>N</th><th>%</th><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>N</th></tr><tr><td>1</td><td>2</td><td>6</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>3</td><td>-</td><td>-</td><td>4/31</td><td>13</td><td>2.9</td><td>0.7</td><td>17</td></tr><tr><td>6</td><td>-</td><td>-</td><td>5/30</td><td>17</td><td>2.5</td><td>0.7</td><td>7</td></tr><tr><td>12</td><td>5</td><td>14.7</td><td>4/30</td><td>13</td><td>2.8</td><td>0.9</td><td>26</td></tr><tr><td>18</td><td>7</td><td>21</td><td>3/27</td><td>11</td><td>-</td><td>-</td><td>-</td></tr></table></td><td>Patients identified at common point: 1

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 1

Targeting strategy defined: 0

Total: 3

Notes:</td></tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>SPECT

Severity of disease:
3 vessel: n=34;
CCS mean 3.5±0.5</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Lee
2000

#1580</td><td>Geographic Location: New York, NY

Number of centers: 1

Dates of data collection: 12/96-4/98

Technology: TMR alone

Type of laser used: Excimer

Number of channels: 41±16

Consecutive enrollment: NR

Length of follow-up: 12 months</td><td>N overall:
15

N women:
4

Mean age:
63±12 years

Age range: 42-79 years

Race: NR

Angina Class
III: 6
IV: 9</td><td>Inclusion Criteria:
CAD not amenable to PTCA/CABG;
Reversible myocardial ischemia; CCS class III/IV angina refractory to medical therapy

Exclusion Criteria:
CVA or MI < 6 wks
Coumadin
Infection
CHF
Severe COPD
USA requiring IV meds
Hospitalization < 2 wks

History (n)
Diabetes: 10

Hyperlipidemia: NR

Hypertension: 9

Family History: NR

Prior MI: 12

Pre-operative unstable angina: NR

Prior PCI/ CABG:</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th colspan="2">Angina Class</th><th colspan="2">Exercise duration (min)</th><th colspan="2">Weekly nitroglycerin usage</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>Mean</th><th>SD</th><th>Mean</th><th>SD</th></tr><tr><td>1</td><td>1</td><td>6.6</td><td>1.6</td><td>0.6</td><td>8.0</td><td>3.9</td><td>5.2</td><td>2.6</td></tr><tr><td>3</td><td>-</td><td>-</td><td>1.5</td><td>0.8</td><td>8.5</td><td>4.4</td><td>3.8</td><td>1.7</td></tr><tr><td>6</td><td>2</td><td>13.3</td><td>1.9</td><td>0.9</td><td>-</td><td>-</td><td>3.8</td><td>1.5</td></tr><tr><td>12</td><td>2</td><td>13.3</td><td>1.8</td><td>0.8</td><td>9.0</td><td>3.9</td><td>1.7</td><td>0.5</td></tr></table></td><td>Patients identified at common point: 1

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 1

Targeting strategy defined: 0

Total: 3

Notes:</td></tr>
</table>

Study	Design	No. of Patients	Patient Population	Outcomes	Quality Score
			8/12 P.V.D: NR Exam Ejection Fraction: 38%±8% LVEF < 30%: none Objective evidence of ischemia: Thallium SPECT Severity of disease: CCS mean 3.5±0.5		

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr>
<td>Muxi 2003

#1740</td>
<td>Geographic Location: Spain

Number of centers: 1

Dates of data collection:

Technology:
TMR alone
TMR with CABG
PMR

Type of laser used: holmium:YAG

Number of channels: 34 +/-14

Consecutive enrollment: Yes

Length of follow-up: 12 months</td>
<td>N overall: 16

N women:4

Mean age: 60 +/-8

Age range: NR

Race: NR

Angina Class
III: NR
IV: NR</td>
<td>Inclusion Criteria:
Class III/IV angina
Not candidates for PCI/CABG

Exclusion Criteria: NR

History (n)
Diabetes: 6

Hyperlipidemia: 12

Hypertension: 8

Family History: NR

Prior MI: NR

Pre-operative unstable angina: NR

Prior PCI/ CABG: 11

P.V.D: NR

Exam
Ejection Fraction:
Mean 57% +/-13%

LVEF < 30%: NR

Objective evidence of ischemia:
Dipyridamole Tetrofosmin scan

Severity of disease:
1 v dz: 2
2 v dz: 3</td>
<td>Symptom Status

Intervention
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class</th></tr>
<tr><th>N</th><th>%</th><th>Mean</th><th>SD</th></tr>
<tr><td>1</td><td>16/16</td><td>100</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>16/16</td><td>100</td><td>1.63</td><td>0.72</td></tr>
<tr><td>6</td><td>15/16</td><td>94</td><td>1.8</td><td>0.86</td></tr>
<tr><td>12</td><td>15/16</td><td>94</td><td>1.93</td><td>0.8</td></tr>
</table>
</td>
<td>Patients identified at common point: 1

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 2

Notes:</td>
</tr>
</table>

Study	Design	No. of Patients	Patient Population	Outcomes	Quality Score
			3 v dz: 11		

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr>
<td>Nagele 1998

#1610</td>
<td>Geographic Location: Hamburg, Germany

Number of centers: 1

Dates of data collection: NR

Technology: TMR alone

Type of laser used: CO2

Number of channels: 33

Consecutive enrollment: Yes

Length of follow-up: 3 years</td>
<td>N overall: 60

N women: 19

Mean age: 63.9±7.6 years

Age range: NR

Race: NR

Angina Class
III: NR
IV: NR</td>
<td>Inclusion Criteria: Refractory angina judged unsuitable for conventional procedures and not responsive to increase in med rx

Exclusion Criteria: NR

History (%)
Diabetes: 18 (29.9%)

Hyperlipidemia: 36 (60%)

Hypertension: 37 (62%)

Family History: NR

Prior MI: 34 (56.7%)

Pre-operative unstable angina: NR

Prior PCI/ CABG: 14 (23.3%)/ 47 (78.3%)

P.V.D: NR

Exam
Ejection Fraction: 53.6%±15%

LVEF < 30%: NR

Objective evidence of ischemia: Sestamibi</td>
<td>Symptom Status

Intervention
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th colspan="2">Angina Class</th></tr>
<tr><th>N</th><th>%</th><th>Mean</th><th>SD</th></tr>
<tr><td>1</td><td>7</td><td>12</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>-</td><td>-</td><td>1.8</td><td>0.8</td></tr>
<tr><td>6</td><td>-</td><td>-</td><td>2.0</td><td>0.9</td></tr>
<tr><td>12</td><td>14</td><td>23</td><td>2.3</td><td>1.0</td></tr>
<tr><td>24</td><td>-</td><td>-</td><td>2.5</td><td>1.1</td></tr>
<tr><td>36</td><td>16</td><td>26.7</td><td>2.6</td><td>0.9</td></tr>
</table></td>
<td>Patients identified at common point: 1

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 1

Targeting strategy defined: 0

Total: 3

Notes:</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Severity of disease:
CCS mean 3.3±0.5</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Peterson 2003 #20</td><td>Geographic Location: USA

Number of centers: 173

Dates of data collection: 1/98-12/01

Technology: TMR alone

Type of laser used: NR

Number of channels: NR

Consecutive enrollment: NR

Length of follow-up: NR</td><td>N overall: 661

Women: 30%

Mean age: 62±11 years

Age range: NR

Race: NR

Angina Class
III: 32%
IV: 46%</td><td>Inclusion Criteria:
All patients in STS database with TMR

Exclusion Criteria: NR

History (%)
Diabetes: 49%

Hyperlipidemia: 74%

Hypertension: 76%

Family History: 45%

Prior MI: 53%

Pre-operative unstable angina: NR

Prior PCI/ CABG: 91%

P.V.D: NR

Exam
Ejection Fraction: 46%±13%

LVEF ≤ 45%: 42%

Objective evidence of ischemia: NR

Severity of disease: NR</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th></tr><tr><th>N</th><th>%</th></tr><tr><td>1</td><td>-</td><td>6.4</td></tr></table>
TMR with CABG data reported in separate table</td><td>Patients identified at common point: 1

Sufficient follow-up: 0

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 1

Targeting strategy defined: 0

Total: 2

Notes:</td></tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Schneider 2001

#1560</td><td>Geographic Location: Leipzig, Germany

Number of centers: 1

Dates of data collection: 3/96-2/99

Technology: TMR alone

Type of laser used: Holmium:YAG

Number of channels: 23±6

Consecutive enrollment: Yes

Length of follow-up: 36 months</td><td>N overall: 14

N women: 3

Mean age: 64.5±5 years

Age range: NR

Race: NR

Angina Class
III: NR
IV: NR</td><td>Inclusion Criteria: Class III/IV refractory to medical therapy; Presence of areas of reversible ischemia; Ineligible for CABG/PTCA

Exclusion Criteria: LVEF < 25%; USA; MI < 6 months

History (n)
Diabetes: NR

Hyperlipidemia: NR

Hypertension: NR

Family History: NR

Prior MI: 8

Pre-operative unstable angina: NR

Prior PCI: 4

Prior CABG: 6

P.V.D:NR

Exam
Ejection Fraction: 52.2%±10%</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th colspan="2">Angina Class</th><th colspan="2">Exercise capacity (W)</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>Mean</th><th>SD</th></tr><tr><td>1</td><td>0</td><td>0</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>6</td><td>-</td><td>-</td><td>1.6</td><td>0.7</td><td>102.1</td><td>17</td></tr><tr><td>12</td><td>-</td><td>-</td><td>1.6</td><td>0.7</td><td>100</td><td>16</td></tr><tr><td>18</td><td>-</td><td>-</td><td>1.7</td><td>0.5</td><td>91.7</td><td>13</td></tr><tr><td>24</td><td>-</td><td>-</td><td>2.3</td><td>0.9</td><td>91.7</td><td>20</td></tr><tr><td>36</td><td>5</td><td>36</td><td>2.4</td><td>1.1</td><td>85</td><td>22</td></tr></table>
TMR with CABG data reported in separate table</td><td>Patients identified at common point: 1

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 2

Notes:</td></tr>
</table>

Study	Design	No. of Patients	Patient Population	Outcomes	Quality Score
			LVEF < 30%: NR Objective evidence of ischemia: dipyridamole thallium Severity of disease: NR		

Transmyocardial Revascularization with CABG – Randomized Controlled Trials

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr>
<td>Allen 2000

#410</td>
<td>Geographic Location: US

Number of centers: 24

Dates of data collection: 1996-1997

Technology: TMR with CABG

Type of laser used: Holmium

Number of channels: 25+/- 10

Consecutive enrollment: Yes

Length of follow-up: 1 yr

Control: CABG alone</td>
<td>N overall: 263

N int: 132
N con:131

N women: 118

Mean age: 63.5

Age range: NR

Race: NR

Angina Class
III: NR
IV: NR</td>
<td>Inclusion Criteria:
Not amenable to complete CABG; Viable myocardium

Exclusion Criteria:
Severe COPD;
NQWMI < 3 wks enrollment;
Severe arrhythmia;
Decompensated HF

History (n intervention)
Diabetes: 91

Hyperlipidemia: NR

Hypertension: NR

Family History: NR

Prior MI: 90

Pre-operative unstable angina: NR

Prior CABG: 40

P.V.D: 30

Exam (intervention)
Ejection Fraction (mean): 51%

LVEF < 30%: NR

Objective evidence of ischemia: NR

Severity of disease: NR</td>
<td>Symptom Status

Intervention
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class reduction</th><th>Exer time (min)</th></tr>
<tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>Mean</th></tr>
<tr><td>1</td><td>130*</td><td>98.5</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>-</td><td>-</td><td>0.4</td><td>-</td><td>-</td></tr>
<tr><td>6</td><td>120</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>12</td><td>84</td><td>95</td><td>0.5</td><td>-</td><td>6.1</td></tr>
</table>
Control
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class</th><th>Exer time (min)</th></tr>
<tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>Mean</th></tr>
<tr><td>1</td><td>121</td><td>92.4</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>-</td><td>-</td><td>-</td><td>0.4</td><td>-</td><td>-</td></tr>
<tr><td>6</td><td>108</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>12</td><td>80</td><td>89</td><td>0.6</td><td>-</td><td>5.6</td></tr>
</table>
*p=0.02</td>
<td>Randomization described and appropriate: 1

Double-blinding described and appropriate: 1

Withdrawals/ drop-outs described: 1

Targeting strategy defined: 0

Total: 3

Notes:</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr>
<td>Gregoric 2003

#1770</td>
<td>Geographic Location: US

Number of centers: 1

Dates of data collection: 2000-2001

Technology: TMR with off pump CABG

Type of laser used: CO2

Number of channels: 37

Consecutive enrollment: Yes

Length of follow-up: 6 months</td>
<td>N overall: 17
N women: 9

Mean age: 63

Age range: 44-85

Race: NR

Angina Class
III: 4
IV: 13</td>
<td>Inclusion Criteria: NR

Exclusion Criteria: NR

History (n)
Diabetes: 12

Hyperlipidemia:

Hypertension: 16

Family History: NR

Prior MI: 12

Pre-operative unstable angina: NR

Prior CABG: 16

P.V.D: NR

Exam
Ejection Fraction: NR

LVEF<35%: n=12

Objective evidence of ischemia: NR

Severity of disease:
3-v dz: 6
4-v dz: 3</td>
<td>Symptom Status

Intervention
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class</th></tr>
<tr><th>N</th><th>%</th><th>Mean</th><th>SD</th></tr>
<tr><td>1</td><td>16</td><td>94</td><td>-</td><td>-</td></tr>
<tr><td>6</td><td>16</td><td>94</td><td>0.1</td><td>-</td></tr>
</table>
</td>
<td>Patients identified at common point: 1

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 1

Total: 3

Notes:</td>
</tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr>
<td>Guleserian 2003

#1750</td>
<td>Geographic Location: US

Number of centers: 1

Dates of data collection: 2/2000-3/02

Technology: TMR alone; TMR with CABG

Type of laser used: holmium:YAG

Number of channels: 30 +/- 9 with TMR alone; 17+/66 with TMR+CABG

Consecutive enrollment: Yes

Length of follow-up: 18 months</td>
<td>N overall: 81 (34 TMR alone; 47 TMR+CABG)

N women: 35

Mean age: 61 +/- 11

Age range: 34-85

Race: NR

Angina Class III: NR
IV: NR</td>
<td>Inclusion Criteria: NR

Exclusion Criteria: NR

Note: Patient characteristic data not provided by intervention group. Numbers below are aggregate numbers for patients receiving TMR alone and patients receiving TMR plus CABG.

History (n)
Diabetes: 48 (59%)

Hyperlipidemia: 64 (79%)

Hypertension: 71 (88%)

Family History: NR

Prior MI: 57 (70%)

Pre-operative unstable angina: 30 (37%)

Prior CABG: 42(52%)

P.V.D: NR</td>
<td>Symptom Status

TMR alone
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Seattle phys limitation</th><th colspan="2">Seattle angina freq</th><th colspan="2">Seattle disease percept</th></tr>
<tr><th>N</th><th>%</th><th>Score</th><th>SD</th><th>Score</th><th>SD</th><th>Score</th><th>SD</th></tr>
<tr><td>1</td><td>31/34</td><td>91</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>18</td><td>-</td><td>-</td><td>39</td><td>25</td><td>53</td><td>34</td><td>48</td><td>27</td></tr>
</table>
TMR + CABG
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Seattle phys limitation</th><th colspan="2">Seattle angina freq</th><th colspan="2">Seattle disease percept</th></tr>
<tr><th>N</th><th>%</th><th>Score</th><th>SD</th><th>Score</th><th>SD</th><th>Score</th><th>SD</th></tr>
<tr><td>1</td><td>45/47</td><td>96</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>18</td><td>-</td><td>-</td><td>71</td><td>26</td><td>94</td><td>23</td><td>88</td><td>20</td></tr>
</table>
18-month survival 62/81 (77%) for combined groups and was not significantly different.
This study should be considered a trial without randomization.</td>
<td>Patients identified at common point: 1

Sufficient follow-up: 0

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 1

Notes:
Evident that all available data not reported in paper.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Exam
Ejection Fraction:
Mean 44% +/- 14%

LVEF < 30%: NR

Objective evidence of ischemia: NR

Severity of disease:
3 v dz: 46 (57%)
LM dz: 11 (14%)</td><td></td><td></td></tr>
<tr><td>Peterson 2003

#20</td><td>Geographic Location: USA

Number of centers: 173

Dates of data collection: 1/98-12/01

Technology: TMR with CABG

Type of laser used: NR

Number of channels: NR

Consecutive enrollment: NR

Length of follow-up: NR</td><td>N overall: 2475

Women: 27%

Mean age: 65±10 years

Age range: NR

Race: NR

Angina Class
III: 35%
IV: 23%</td><td>Inclusion Criteria:
All patients in STS database with TMR+CABG

Exclusion Criteria:
NR

History (%)
Diabetes: 50%

Hyperlipidemia: 68%

Hypertension: 76%

Family History: 43%

Prior MI: 50%

Pre-operative unstable angina: NR

Prior PCI/ CABG: 43%

P.V.D: NR

Exam
Ejection Fraction:
50%±14%</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th></tr><tr><th>N</th><th>%</th></tr><tr><td>1</td><td>-</td><td>4.2</td></tr></table>
Note: Data on TMR conducted alone reported in separate table</td><td>Patients identified at common point: 1

Sufficient follow-up: 0

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 1

Targeting strategy defined: 0

Total: 2

Notes:</td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>LVEF ≤ 45%: 37%

Objective evidence of ischemia: NR

Severity of disease: NR</td><td></td><td></td></tr>
<tr><td>Schneider 2001

#1560</td><td>Geographic Location: Leipzig, Germany

Number of centers: 1

Dates of data collection: 3/96-2/99

Technology: TMR with CABG

Type of laser used: Holmium:YAG

Number of channels: 16±6

Consecutive enrollment: Yes

Length of follow-up: 36 months</td><td>N overall: 27

N women: 13

Mean age: 63.9±8 years

Age range: NR

Race: NR

Angina Class
III: NR
IV: NR</td><td>Inclusion Criteria:
Class III/IV refractory to medical therapy;
Presence of areas of reversible ischemia;
Eligible for CABG

Exclusion Criteria: LVEF < 25%; USA;
MI < 6 months

History (n)
Diabetes: NR

Hyperlipidemia: NR

Hypertension: NR

Family History: NR

Prior MI: 21

Pre-operative unstable angina: NR

Prior PCI: 10

Prior CABG: 11

P.V.D:NR

Exam
Ejection Fraction:</td><td>Symptom Status

TMR with CABG
<table><tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th colspan="2">Angina Class</th><th colspan="2">Exercise capacity (W)</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>Mean</th><th>SD</th></tr><tr><td>1</td><td>0</td><td>0</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>6</td><td>-</td><td>-</td><td>1.6</td><td>0.9</td><td>100</td><td>29</td></tr><tr><td>12</td><td>-</td><td>-</td><td>1.5</td><td>0.8</td><td>106</td><td>36</td></tr><tr><td>18</td><td>-</td><td>-</td><td>1.4</td><td>0.9</td><td>100</td><td>40</td></tr><tr><td>24</td><td>-</td><td>-</td><td>1.6</td><td>0.8</td><td>92.9</td><td>40</td></tr><tr><td>36</td><td>3</td><td>11</td><td>1.7</td><td>0.5</td><td>95</td><td>33</td></tr></table>
TMR alone data reported in separate table</td><td>Patients identified at common point: 1

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 2

Notes:</td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>51%±12%

LVEF < 30%: NR

Objective evidence of ischemia: dipyridamole thallium

Severity of disease: NR</td><td></td><td></td></tr>
<tr><td>Stamou 2002

#100</td><td>Geographic Location: Washington, DC

Number of centers: 1

Dates of data collection: 3/96-2/00

Technology: TMR with CABG

Type of laser used: CO_2 / Holmium:YAG

Number of channels: 23.7±8.6

Consecutive enrollment: Yes

Length of follow-up: 12 months</td><td>N overall: 169

N women: 50

Mean age: 62.6±9.6

Age range: NR

Race: NR

Angina Class III/IV: 152</td><td>Inclusion Criteria: Intractable angina and ≥1 major vessel or branch not amenable to surgical revascularization; Presence of viable myocardium surrounding nongraftable areas

Exclusion Criteria: Recent MI within previous week before surgery; Severe arrhythmias; Decompensated heart failure

History (n)
Diabetes: 89

Hyperlipidemia: NR

Hypertension: 129

Family History: 116

Prior MI: 108

Pre-operative unstable angina: 106</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th colspan="2">Angina Class III/IV</th></tr><tr><th>N</th><th>%</th><th>N</th><th>%</th></tr><tr><td>3</td><td>-</td><td>-</td><td>5</td><td>3</td></tr><tr><td>6</td><td>-</td><td>-</td><td>7</td><td>4</td></tr><tr><td>12</td><td>24</td><td>15</td><td>7</td><td>4</td></tr></table>
In-hospital mortality 14/169 (8.3%)</td><td>Patients identified at common point: 1

Sufficient follow-up: 0

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 1

Notes:</td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Prior PCI/ CABG: 160

P.V.D: NR

Exam (n)
Ejection Fraction: NR

LVEF < 35%: 27

Objective evidence of ischemia: NR

Severity of disease: NR</td><td></td><td></td></tr>
<tr><td>Wehberg 2003

#1850</td><td>Geographic Location: Salisbury, MD, USA

Number of centers: 1

Dates of data collection: Unspecified 6 month period

Technology: TMR with CABG

Type of laser used: Holmium:YAG

Number of channels: NR

Consecutive enrollment: Yes</td><td>N overall: 255
CABG: 219
TMR + CABG: 36

N women: NR

Mean age:
CABG: 65.4±1.4 yrs
TMR/CABG: 63.3±1.6 yrs

Age range: NR

Race: NR

Angina Class (mean):
CABG: 3.5
TMR/CABG: 3.4</td><td>Inclusion Criteria:
CCS III/IV; Severe 3-vessel CAD, EF≥30%

Exclusion Criteria:
Required emergency revascularization procedure within 12 hours; diagnosed acute MI within 72 hours; persistent unstable angina despite continuous intravenous treatment

History (n)
Diabetes: NR

Hyperlipidemia: NR

Hypertension: NR

Family History: NR

Prior MI: NR

Pre-operative unstable</td><td>Symptom Status

CABG only
<table><tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th>Angina Class</th></tr><tr><th>N</th><th>%</th><th>Mean</th></tr><tr><td>1</td><td>-</td><td>2.3</td><td>0.3</td></tr></table>
TMR + CABG
<table><tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th>Angina Class</th></tr><tr><th>N</th><th>%</th><th>Mean</th></tr><tr><td>1</td><td>0</td><td>0*</td><td>0.4</td></tr></table>
*p=0.80</td><td>Patients identified at common point: 1

Sufficient follow-up: 0

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 1

Notes:</td></tr>
</table>

Study	Characteristics	No. of Patients	Patient Population	Outcomes	Quality Score
	Length of follow-up: 1 month		angina: NR Prior CABG: CABG: 5.5% TMR/CABG: 11.1% P.V.D: NR Exam (n) Ejection Fraction: CABG: 48.5±1.6% TMR/CABG: 51.6±0.9% LVEF < 35%: NR Objective evidence of ischemia: NR Severity of disease: 3 vessel disease with diameter lumen reduction ≥ 75%		

Percutaneous Myocardial Revascularization – Randomized Controlled Trials

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr>
<td>DIRECT 2001

#1820</td>
<td>Geographic Location: USA

Number of centers: Multi-center

Dates of data collection: NR

Technology: PMR

Type of laser used: Holmium-YAG

Number of channels:
Low Dose (LD): 10-15
High dose (HD): 20-25

Consecutive enrollment: NR

Length of follow-up: 12 months

Control: Placebo (sham procedure)</td>
<td>N overall: 298
N LD: 98
N HD: 98
N con: 102

N women: NR (predominantly male)

Mean age: 63 years

Age range: NR

Race: NR

Angina Class
III: NR
IV: NR</td>
<td>Inclusion Criteria: Known coronary disease; Severe symptoms despite medical therapy; Not eligible for PTCA or bypass with reproducible positive exercise tests associated with angina; Reversible ischemia

Exclusion Criteria: NR

History (n intervention)
Diabetes: NR

Hyperlipidemia: NR

Hypertension: NR

Family History: NR

Prior MI: NR

Pre-operative unstable angina: NR

Prior PCI/ CABG: NR

P.V.D: NR

Exam (intervention)
Ejection Fraction: approx. 50%

LVEF < 30%: NR</td>
<td>Symptom Status

High Dose (20-25 channels)
<table>
<tr><th rowspan="2">Month</th><th colspan="2">MACE-free Survival</th><th>Angina Class III/IV</th><th>Change in Exercise time (sec)</th><th>Major Adverse Coronary Events (MACE)</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>Mean</th><th>%</th></tr>
<tr><td>1</td><td>-</td><td>95.9</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>6</td><td>-</td><td>-</td><td>35</td><td>26.9</td><td>10.2</td></tr>
<tr><td>12</td><td>-</td><td>78.6</td><td>-</td><td>-</td><td>-</td></tr>
</table>
Low Dose (10-15 channels)
<table>
<tr><th rowspan="2">Month</th><th colspan="2">MACE-free Survival</th><th>Angina Class III/IV</th><th>Change in Exercise time (sec)</th><th>Major Adverse Coronary Events (MACE)</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>Mean</th><th>%</th></tr>
<tr><td>1</td><td>-</td><td>91.8</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>6</td><td>-</td><td>-</td><td>47</td><td>34.9</td><td>9.2</td></tr>
<tr><td>12</td><td>-</td><td>85.7</td><td>-</td><td>-</td><td>-</td></tr>
</table>
Control (Placebo/Sham procedure)
<table>
<tr><th rowspan="2">Month</th><th colspan="2">MACE-free Survival</th><th>Angina Class III/IV</th><th>Change in Exercise time (sec)</th><th>Major Adverse Coronary Events (MACE)</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>Mean</th><th>%</th></tr>
<tr><td>1</td><td>-</td><td>100</td><td>-</td><td>-</td><td>0</td></tr>
<tr><td>6</td><td>-</td><td>-</td><td>44</td><td>30.7</td><td>8.8</td></tr>
<tr><td>12</td><td>-</td><td>88.7</td><td>-</td><td>-</td><td>-</td></tr>
</table>
• Mortality “similar” among the three groups
• Higher incidence of non-Q wave MI in laser groups
• Higher incidence of repeat revascularization in high-dose group
• At 12 months >40% of all patients had ≥2 class improvement in angina</td>
<td>Randomization described and appropriate: N/A

Double-blinding described and appropriate: N/A

Withdrawls/ drop-outs described: N/A

Targeting strategy defined: N/A

Total: N/A

Notes:
Due to lack of a formalized report of this study, there was not enough information available to assign a quality score.

DIRECT is a follow-up to a Phase I safety and efficacy study, results reported in Kornowski, 2000 (#1350).</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Objective evidence of ischemia: SPECT.

Severity of disease: “Severe”</td><td>• At 6 months no differences that would suggest a therapeutic effect in magnitude of ischemia measured by SPECT at rest or stress.</td><td></td></tr>
<tr><td>Gray 2003

#1210</td><td>Geographic Location: UK

Number of centers: 1

Dates of data collection: 1997-2000

Technology: PMR

Type of laser used: holmium (Cardiogenesis)

Number of channels: NR

Consecutive enrollment: Yes

Length of follow-up: 1 year

Control: medical therapy</td><td>N overall: 73
N int:36
N con:37

N women: 3

Mean age: 61

Age range: 43-72

Race: NR

Angina Class
III: 48
IV:25</td><td>Inclusion Criteria:
Refractory Class III/IV angina
Ischemia on thallium
EF > 25%
Target myocardial wall thickness 8+ mm
Not amenable to PCI/CABG

Exclusion Criteria:
QWMI < 3 months; NQWMI < 6 wks; USA ; Change in meds < 2 wks; Significant arrhythmias; HF; PVD; AS; renal failure; LV thrombus

History (n intervention)
Diabetes:7

Hyperlipidemia: 32

Hypertension: 21

Family History: 26

Prior MI: 26

Pre-operative unstable angina: 0

Prior PCI/ CABG: 35</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th>Change in Exer time</th><th colspan="2">2+ angina class improvement</th></tr><tr><th>N</th><th>%</th><th>sec</th><th>N</th><th>%</th></tr><tr><td>1</td><td>36</td><td>100</td><td>-</td><td>-</td><td>-</td></tr><tr><td>3</td><td>35</td><td>97</td><td>+102*</td><td>5/31**</td><td>16</td></tr><tr><td>6</td><td>35</td><td>97</td><td>-</td><td>-</td><td>-</td></tr><tr><td>12</td><td>35</td><td>97</td><td>+109*</td><td>9/25*</td><td>36</td></tr></table>
Control
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th>Change in Exer time</th><th colspan="2">2+ angina class improvement</th></tr><tr><th>N</th><th>%</th><th>sec</th><th>N</th><th>%</th></tr><tr><td>1</td><td>36</td><td>97</td><td>-</td><td>-</td><td>-</td></tr><tr><td>3</td><td>36</td><td>97</td><td>-26</td><td>0/34</td><td>0</td></tr><tr><td>6</td><td>36</td><td>97</td><td>-</td><td>-</td><td>-</td></tr><tr><td>12</td><td>36</td><td>97</td><td>-62</td><td>0/24</td><td>0</td></tr></table>
*p<0.01
**p=0.02</td><td>Randomization described and appropriate: 1

Double- blinding described and appropriate: 0

Withdrawals/ dropouts described: 1

Targeting strategy defined: 1

Total: 3

Notes: 21 of the 73 patients reported in this paper were included in the data of the PACIFIC trial (Oesterle #1450)</td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>P.V.D: 0

Exam (intervention)
Ejection Fraction: 48%

LVEF < 30%: NR

Objective evidence of ischemia: Thallium

Severity of disease: NR</td><td></td><td></td></tr>
<tr><td>Oesterle 2000

#1450</td><td>Geographic Location:
US and UK

Number of centers: 13

Dates of data collection:
NR

Technology:
PMR

Type of laser used:
Holmium (Eclipse)

Number of channels:
median 15
(8-35)

Consecutive enrollment: Yes

Length of</td><td>N overall: 221
N int: 110
N con:111

N women:
31

Median age:
62

Age range:
38-90

Race:
NR

Angina Class
III: 135
IV:86</td><td>Inclusion Criteria:
Class III/IV angina; Reversible ischemia; LVEF >=30%

Exclusion Criteria:
Exer tolerance not limited by angina; Symptomatic HF; Rx with >80mg lasix QD; LVEF < 8 mm; Renal insufficiency; AS; PVD; LV thrombus; Signif ventricular arrhythmias; USA; Angina meds adjusted < 2 wks; Transmural MI < 3 months; NQWMI < 6 wks

History (n intervention)
Diabetes: 53

Hyperlipidemia: 78</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th>Exercise Time (sec)</th><th colspan="2">2+ angina class improvement</th></tr><tr><th>N</th><th>%</th><th>Mean Change</th><th>N</th><th>%</th></tr><tr><td>12</td><td>102</td><td>93</td><td>+89*</td><td>42/92**</td><td>46</td></tr></table>
Control
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th>Exercise time (sec)</th><th colspan="2">2+ angina class improvement</th></tr><tr><th>N</th><th>%</th><th>Mean Change</th><th>N</th><th>%</th></tr><tr><td>12</td><td>108</td><td>97</td><td>+12.5</td><td>11/99</td><td>11</td></tr></table>
*p=0.008
**data based on investigators' unmasked assessments. Masked assessments showed higher angina class, but still resulted in significantly lower angina class when compared to control (p=0.02)</td><td>Randomization described and appropriate: 1

Double-blinding described and appropriate: 0

Withdrawals/ drop-outs described: 1

Targeting strategy defined: 0

Total: 2

Notes:
30d mortality not directly reported</td></tr>
</table>

Study	Characteristics	No. of Patients	Patient Population	Outcomes	Quality Score
	follow-up: 1 yr		Hypertension: 75 Family History: 70 Prior MI: 71 Pre-operative unstable angina: 0 Prior PCI/ CABG: 95 P.V.D: 0 Exam intervention) Ejection Fraction (median): 50% LVEF < 30%: NR Objective evidence of ischemia: Dipyridamole thallium Severity of disease: NR		
Salem 2004 #1810	Geographic Location: Norway Number of	N overall: 82 N int: 40 N con: 42 N women:	Inclusion Criteria: Not suitable for conventional revascularization, stable CCS III/IV	*Symptom Status* Intervention	Randomization described and appropriate: 1 Double- blinding

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr>
<td></td>
<td>centers: 2

Dates of data collection: 1999-2000

Technology: PMR

Type of laser used: CardioGenesis

Number of channels: 19±4.5

Consecutive enrollment: Yes

Length of follow-up: 12 months</td>
<td>7

Mean age: 66

Age range: NR

Race: NR

Angina Class
III: 71
IV: 11</td>
<td>angina refractory to maximally tolerated medication; reversible ischemia; EF≥ 25% and wall thickness ≥ 8 mm.

Exclusion Criteria: Recent AMI; symptomatic CHF; significant arrhythmias; ventricular thrombus; significant PVD; aortic stenosis or mechanical aortic prostesis; unstable angina requiring hospitalization within 14 days or change of medication.

History (n intervention)
Diabetes: 5

Hyperlipidemia: NR

Hypertension: 19

Family History: 28

Prior MI: 25

Pre-operative unstable angina: None (excluded)

Prior PCI/ CABG: 36

P.V.D: NR</td>
<td>
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Improvement ≥1 class</th><th colspan="2">Improvement ≥2 class</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>%</th><th>N</th><th>%</th></tr>
<tr><td>1</td><td>40</td><td>100</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>40</td><td>100</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>6</td><td>40</td><td>100</td><td>39</td><td>63*</td><td>39</td><td>40***</td></tr>
<tr><td>12</td><td>40</td><td>100</td><td>39</td><td>63**</td><td>39</td><td>35**</td></tr>
</table>
Control
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Improvement ≥1 class</th><th colspan="2">Improvement ≥2 class</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>%</th><th>N</th><th>%</th></tr>
<tr><td>1</td><td>41</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>40</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>6</td><td>40</td><td>-</td><td>40</td><td>36</td><td>40</td><td>12</td></tr>
<tr><td>12</td><td>40</td><td>95</td><td>40</td><td>38</td><td>40</td><td>14</td></tr>
</table>
*p=0.03
**p=0.04
***p<0.01
</td>
<td>described and appropriate: 1

Withdrawals/ dropouts described: 1

Targeting strategy defined: 1

Total: 4

Notes:</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Exam
Ejection Fraction: 64%±12%

LVEF < 30%: NR

Objective evidence of ischemia: Exercise testing or technetium sestamibi stress myocardial perfusion scanning

Severity of disease: NR</td><td></td><td></td></tr>
<tr><td>Stone 2002

#70</td><td>Geographic Location: US

Number of centers: 17

Dates of data</td><td>N overall: 141
N int: 71
N con: 70

N women: 28</td><td>Inclusion Criteria: Class III/IV angina; Failed PCI of chronic total occlusion; No other lesions for PCI/CABG; Viability by thallium,</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">2+ angina class improvement</th><th>Exer time</th></tr><tr><th>N</th><th>%</th><th>N</th><th>%</th><th>sec</th></tr></table></td><td>Randomization described and appropriate: 1

Double-blinding described and appropriate: 1</td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr>
<td></td>
<td>collection: NR

Technology: PMR

Type of laser used: Holmium (Eclipse)

Number of channels: 20 (15-25)

Consecutive enrollment: Yes

Length of follow-up: 6 months</td>
<td>Mean age: 65

Age range: 54-72

Race: NR

Angina Class
III: 88
IV: 53</td>
<td>echo, RNA, or LV gram;
Wall thickness >=9mm

Exclusion Criteria:
LVEF<30%;
Mi < 3 months;
LV aneurysm;
Mural thrombus;
AS, AI, or prosthetic Ao Valve;
Decompensated HF;
VT/VF < 1 wk;
Unable to do baseline ETT;
PCI < 6 wks;
Noncardiac condition limiting life expectancy < 1 yr;
In other study
Unable/unwilling to do f/u testing

History (n intervention)
Diabetes:29

Hyperlipidemia: NR

Hypertension: 50

Family History: NR

Prior MI: 46

Pre-operative unstable angina: NR

Prior CABG: 60

P.V.D: NR</td>
<td>
<table>
<tr><td>In-hospital</td><td>71/71</td><td>100</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>-</td><td>-</td><td>-</td><td>56*</td><td>-</td></tr>
<tr><td>6</td><td>65/71</td><td>91.4</td><td>-</td><td>49**</td><td>+86</td></tr>
</table>

Control
<table>
<tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">2+ angina class improvement</th><th>Exer time</th></tr>
<tr><th>N</th><th>%</th><th>N</th><th>%</th><th>sec</th></tr>
<tr><td>In-hospital</td><td>69/70</td><td>98.6</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3</td><td>-</td><td>-</td><td>-</td><td>38</td><td>-</td></tr>
<tr><td>6</td><td>64/70</td><td>91.2</td><td>-</td><td>37</td><td>+69</td></tr>
</table>

*p=0.12
**p=0.33
</td>
<td>Withdrawals/ drop-outs described: 0

Targeting strategy defined: 1

Total: 3

Notes:
30 d mortality not directly reported</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>Exam (intervention)
Ejection Fraction (mean): 52%

LVEF < 30%: NR

Objective evidence of ischemia: not standardized

Severity of disease:
3v dz: 55%
Lm dz: 17.4%</td><td></td><td></td></tr>
<tr><td>Whitlow 2003

#1800</td><td>Geographic Location: USA

Number of centers: 20

Dates of data collection: USA

Technology: PMR

Type of laser used: Eclipse holmium YAG

Number of channels: 19±7

Consecutive enrollment: Yes

Length of follow-up: 12 months

Control: medical therapy</td><td>N overall: 130
N int: 64
N con: 166

N women: 56

Mean age: 64

Age range: NR

Race: NR

Angina Class
III: 38
IV: 26</td><td>Inclusion Criteria:
Medically refractory Class III/IV rejected for CABG/PCI, LVEF ≥ 30%, wall thickness ≥ 9 mm, angina during exercise stress test.

Exclusion Criteria:
MI within 3 weeks, comorbid condition that prohibits treadmill, aortic stenosis, mechanical aortic valve, left ventricular thrombus.

History (n intervention)
Diabetes: 30

Hyperlipidemia: 51

Hypertension: 49

Family History: NR</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class</th><th colspan="2">QoL-DASI Improvement</th><th>Improve ≥2class</th><th>Treadmill Time (sec)</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>Mean</th><th>SD</th><th>%</th><th>Mean Change</th></tr><tr><td>6</td><td>-</td><td>-</td><td>2.2*</td><td>-</td><td>-</td><td>-</td><td>-</td><td>+87**</td></tr><tr><td>12</td><td>51</td><td>79.7</td><td>1.9**</td><td>-</td><td>10.0***</td><td>12.9</td><td>55**</td><td>+100**</td></tr></table>
Control
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Angina Class</th><th colspan="2">QoL-DASI Improvement</th><th>Improve ≥2class</th><th>Treadmill Time (sec)</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>Mean</th><th>SD</th><th>%</th><th>Mean Change</th></tr><tr><td>6</td><td>-</td><td>-</td><td>2.6</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-60</td></tr><tr><td>12</td><td>155</td><td>93.4</td><td>2.4</td><td>-</td><td>5.7</td><td>10.3</td><td>31</td><td>-20</td></tr></table></td><td>Randomization described and appropriate: 1

Double-blinding described and appropriate: 0

Withdrawls/ drop-outs described: 1

Targeting strategy defined: 1

Total: 3

Notes:</td></tr>
</table>

Study	Characteristics	No. of Patients	Patient Population	Outcomes	Quality Score
			Prior MI: 43 Pre-operative unstable angina: 3 (on IV NTG) Prior PCI/ CABG: 45/54 P.V.D: NR Exam Ejection Fraction: 47±10 LVEF < 30%: Objective evidence of ischemia: NR Severity of disease: NR	*p=0.003 **p≤0.001 ***p=0.005 Freedom from death given in a Kaplan-Meier curve for 0-12 months. Exact 30-day mortality not reported.	

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Kaul 1999

#660</td><td>Geographic Location: New Delhi, India

Number of centers: 1

Dates of data collection: 6/97-5/98

Technology: PMR

Type of laser used: Holmium:YAG (Eclipse)

Number of channels: 15±5

Consecutive enrollment: Yes

Length of follow-up: NR</td><td>N overall: 35

Women: 17%

Mean age: 62±9 years

Age range: NR

Race: NR

Angina Class
III: 14
IV: 21</td><td>Inclusion Criteria:
CAD no amenable to PTCA/CABG; CCS III/IV despite intensive medical treatment; Inducible ischemia on stress test or unstable angina (ST depression); >9mm wall thickness of left ventricle; EF>0.25%

Exclusion Criteria:
Decompensated HF; Ventricular tachycardia; Ventricular fibrillation; Acute MI within 4 weeks

History (n)
Diabetes: 10

Hyperlipidemia: 14

Hypertension: 15

Family History: 14

Prior MI: 21

Pre-operative unstable angina: NR

Prior PCI/ CABG: 23

P.V.D: NR

Exam
Ejection Fraction: 38%±7%

LVEF < 30%: NR

Objective evidence of ischemia:</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Survival</th><th colspan="2">Dropped ≥2 angina classes</th><th colspan="2">Angina Class</th></tr><tr><th>N</th><th>%</th><th>N</th><th>%</th><th>Mean</th><th>SD</th></tr><tr><td>1</td><td>35/35</td><td>100</td><td>29/35</td><td>83</td><td>0.82</td><td>0.7</td></tr><tr><td>3</td><td>35/35</td><td>100</td><td>25/35</td><td>71</td><td>0.94</td><td>0.65</td></tr><tr><td>6</td><td>-</td><td>-</td><td>19/26</td><td>73</td><td>1.08</td><td>0.58</td></tr></table>
No deaths reported</td><td>Patients identified at common point: 1

Sufficient follow-up: 0

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 0

Total: 1

Notes:</td></tr>
</table>

<table>
<tr><th>Study</th><th>Characteristics</th><th>No. of Patients</th><th>Patient Population</th><th>Outcomes</th><th>Quality Score</th></tr>
<tr><td></td><td></td><td></td><td>NR

Severity of disease:
Triple vessel n=22</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Kornowski 2000

#1310</td><td>Geographic Location: USA

Number of centers: 3

Dates of data collection: NR

Technology: PMR

Type of laser used: Holmium:YAG

Number of channels: 26±10

Consecutive enrollment: NR

Length of follow-up: 6 months</td><td>N overall: 77

N women: 21

Mean age: 61±11 years

Age range: 36-82 years

Race: MR

Angina Class
III: 49
IV: 38</td><td>Inclusion Criteria:
Symptomatic CAD with refractory angina CCS III/IV despite best pharmacological therapy; Poor candidate for PTCA/CABG

Exclusion Criteria:
Severe LVEF<30%; MI < 1 month; PTCA within 4 months; Chronic atrial fibrillation; Major comorbidity

History (n)
Diabetes: 35

Hyperlipidemia: 63

Hypertension: NR

Family History: NR

Prior MI: 44

Pre-operative unstable angina: NR

Prior PCI/ CABG: 47/67

P.V.D: NR

Exam
Ejection Fraction: 48%±11%

LVEF < 30%: NR</td><td>Symptom Status

Intervention
<table><tr><th rowspan="2">Month</th><th colspan="2">Deaths</th><th colspan="2">Angina Class</th><th colspan="2">Dropped ≥2 angina classes</th><th colspan="2">Time to ST-segment depression (sec)</th></tr><tr><th>N</th><th>%</th><th>Mean</th><th>SD</th><th>N</th><th>%</th><th>Mean</th><th>SD</th></tr><tr><td>1</td><td>0</td><td>0</td><td>2.1</td><td>1.1</td><td>-</td><td>-</td><td>400</td><td>172</td></tr><tr><td>3</td><td>-</td><td>-</td><td>-</td><td>-</td><td>25/76</td><td>33</td><td>-</td><td>-</td></tr><tr><td>6</td><td>0</td><td>0</td><td>2.0</td><td>1.1</td><td>27/63</td><td>43</td><td>436</td><td>175</td></tr></table></td><td>Patients identified at common point: 1

Sufficient follow-up: 1

Blinded outcome assessment: 0

Measurement and adjustment for confounders: 0

Targeting strategy defined: 1

Total: 3

Notes:</td></tr>
</table>

Study	Characteristics	No. of Patients	Patient Population	Outcomes	Quality Score
			Objective evidence of ischemia: SPECT Dual isotope Severity of disease: CCS mean 3.3±0.5		