Transmyocardial Revascularization

Description

Transmyocardial revascularization (TMR), also known as transmyocardial laser revascularization, is a surgical technique that attempts to improve blood flow to ischemic heart muscle by creating direct channels from the left ventricle into the myocardium. TMR may be performed via a thoracotomy or percutaneous transmyocardial revascularization (PTMR).

Background

Transmyocardial revascularization (TMR) is performed via a thoracotomy, with the patient under general anesthesia. Cardiopulmonary bypass is not required. A laser probe is placed on the surface of the myocardium, and while the heart is in diastole, the laser is discharged to create a channel through the myocardium into the left ventricle. Less invasive approaches to TMR are also being studied. Various port access procedures are being evaluated to use TMR using novel robotic and thoracoscopic techniques.

TMR can also be performed by the percutaneous route (PTMR). PTMR (now being called percutaneous myocardial channeling or PMC) is a catheter-based system using Ho: YAG laser revascularization under fluoroscopic guidance. It is performed in Europe but is not currently approved by the U.S. Food and Drug Administration (FDA). PTMR is performed by interventional cardiologists, who create myocardial channels with lasers positioned at the endocardial surface inside the left ventricle. Although less invasive than TMR, there are potential disadvantages to the PTMR approach. To minimize the possibility of cardiac tamponade, a potentially fatal condition in which the pericardium fills with blood, the myocardial channels created by PTMR are not as deep as those made by TMR. Also, positioning the laser under fluoroscopic guidance is less precise than the direct visual control of TMR. Less invasive, e.g., robotic techniques for use of this procedure are also being studied.

Open TMR has been investigated in 2 populations of patients: 1) patients with ischemic myocardium who are not candidates for other types of revascularization procedures, such as coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA) due to anatomical features of their coronary circulation; and 2) as an adjunct to CABG in patients with areas of ischemic myocardium that are not amenable to surgical revascularization. Other potential applications of TMR include its use as an adjunct to stem-cell based therapy.
Regulatory Status

The Heart Laser™ received final U.S. Food and Drug Administration (FDA) approval to market in 1998 for the treatment of patients with stable class III or IV angina refractory to medical treatment and secondary to objectively demonstrated coronary artery atherosclerosis not amendable to direct coronary revascularization. The Eclipse TMR 2000™ received FDA approval for similar indications in July 1999. Neither device is approved for use as an adjunct to CABG. Use of either device for this purpose would be considered an off-label indication.

Related Policies

None

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Open transmyocardial laser revascularization may be considered medically necessary for patients with class III or IV angina, who are not candidates for coronary artery bypass graft (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA) surgery who meet ALL of the following criteria:

- Presence of class III or IV angina refractory to medical management.
- Documentation of reversible ischemia.
- Left ventricular ejection fraction >30%.
- No evidence of recent myocardial infarction or unstable angina within the last 21 days.
- No severe comorbid illness such as chronic obstructive pulmonary disease (COPD).

Open transmyocardial laser revascularization may be considered medically necessary as an adjunct to coronary artery bypass grafting (CABG) in those patients with documented areas of ischemic myocardium that are not amenable to surgical revascularization.

Open transmyocardial laser revascularization is considered investigational for all other indications not meeting the above criteria.

Percutaneous transmyocardial laser revascularization is considered investigational.

Rationale

Literature Review

Open Transmyocardial Laser Revascularization

This portion of the policy is based in part on two Technology Evaluation Center (TEC) Assessments, a 1998 Assessment (1) that focused on the use of open transmyocardial laser revascularization
(TMR) as an alternative to inoperable coronary artery disease and a 2001 Assessment (2) that focused on its use as an adjunct to coronary artery bypass surgery (CABG).

Open TMR in Patients with Inoperable Coronary Artery Disease

The 1998 TEC Assessment offered the following observations and conclusions:

- Results of randomized controlled clinical trials suggested that patients with refractory, nonoperable class III or IV angina respond well to TMR. Specifically, results of 1 trial reported that 86% of those assigned TMR were in angina class I or II at 12 months of follow-up compared with 30% in the medical management group. In addition, a decline in the number of hospital admissions favored TMR. The data on morbidity and mortality were inconclusive but were in favor of an equivalent or lower mortality rate with TMR.

Patients enrolled in these trials were carefully selected to maximize the benefit of TMR. All patients had class III or IV angina that was refractory to medical management and objective evidence of reversible ischemia on exercise testing or perfusion scanning. In addition, a variety of exclusion criteria were used to minimize the risk of open thoracotomy. These exclusion criteria varied slightly among the trials and have evolved in response to recognition of high-risk subgroups among the initial randomized controlled trials (RCTs). In general, patients with recent unstable angina or myocardial infarction (MI), an ejection fraction of less than 30%, and severe comorbid illness were excluded from these trials.

The 3 unpublished RCTs cited in the original TEC Assessment (1) have since appeared in the literature. (3-5) Since then, 3 additional RCTs with similar design have been published. Schofield and colleagues (6) randomized 188 patients with refractory angina to TMR via a high-energy CO₂ laser or medical management alone. At 12 months, 25% of the patients assigned to TMR improved by at least 2 Canadian Cardiovascular Society (CCS) anginal classes, compared to only 4% in the medical management group (p<0.001). There were no statistically significant differences in exercise duration, 12-minute walk distance, or radionucleotide perfusion. The number of patients improving by 2 or more angina classes was much less than in the 3 previously cited RCTs. There was 5% perioperative mortality for the TMR group and a lower overall survival at 12 months (89% vs. 96%, p=0.14), but this difference did not reach statistical significance.

Aaberge and others (7) compared 50 patients randomized to pulsed CO₂ laser TMR with 50 patients randomized to medical management. At 12 months, 39% of the patients assigned to TMR improved by at least 2 New York Heart Association (NYHA) anginal classes versus 0% in the medical management group (both the NYHA and CCS contain 4 anginal classes, but class 1 in the NYHA system allows no symptoms, potentially making a 2-class improvement more difficult to achieve). Exercise capacity was not improved by TMR. There was a 4% perioperative mortality rate with lower overall survival at 12 months (88% vs. 92%, respectively, p=NS), but this difference did not reach statistical significance.

Jones et al. (8) randomized 86 patients with refractory angina to TMR with a Ho:YAG laser or to medical management. At 12 months, the TMR group had an average improvement of slightly more than 2 CCS anginal classes over the medical management group. The TMR group also had a
significant improvement in exercise duration (490 vs. 294 seconds, respectively, \( p=0.0002 \)). There was only 1 perioperative death in the TMR group, but overall survival data were not provided. An analysis of registry data evaluated outcomes of TMR in 661 patients who underwent TMR alone for refractory angina. (9, 10) This study reported that many patients undergoing TMR in clinical practice differed from those in the randomized trials, especially in regard to the presence of high-risk factors such as unstable angina or recent MI. Patients with unstable angina undergoing TMR had a 30-day mortality that was almost double that of patients without unstable angina (8.3% vs. 4.3%, respectively, \( p<0.05 \)), while patients with an MI in the last 21 days had a mortality risk that was more than double that of patients without recent MI (13.0% vs. 5.4%, respectively, \( p<0.05 \)). Finally, Allen et al. reported on the 5-year results of his earlier trial (3), which demonstrated at 5 years that the significant anginal relief observed 12 months after sole therapy TMR was sustained long term and continued to be superior to that observed for patients maintained on continued medical management alone. (11)

These additional studies support the conclusions of the TEC Assessment that TMR improves anginal symptoms in patients with refractory angina, compared to medical management, and confirm the need for careful selection of patients undergoing the procedure. These studies differ from the original 3 trials in that fewer patients improved by at least 2 anginal classes, suggesting that the magnitude of benefit may be less than in the first 3 trials. These trials do not provide conclusive evidence on whether TMR improves survival or exercise capacity. The data also reinforce that achieving beneficial outcomes of TMR depends on careful patient selection as follows:

- Patients with class III or IV angina refractory to medical management;
- Documentation of reversible ischemia;
- Left ventricular ejection fraction >30%;
- No evidence of recent MI or unstable angina within the last 21 days; and
- No severe comorbid illness such as chronic obstructive pulmonary disease (COPD).

**Open TMR as an Adjunct to CABG**

The 2001 TEC assessment offered the following observations and conclusions (2):

- The TEC Assessment focused on 2 randomized single-blind trials that compared outcomes of patients who underwent CABG alone versus CABG plus TMR. While the smaller of the 2 trials, enrolling only 42 patients, showed a trend toward an improved perioperative mortality associated with TMR, this outcome reached statistical significance in the second larger trial, enrolling 266 patients. In this trial, perioperative mortality decreased from 7.5% in the control group to 1.5% in the TMR group.
- The scientific basis of the improvement in perioperative mortality is unknown, yet the randomized trial was well designed and conducted at multiple institutions, which supported the conclusions.
- There was no significant improvement in subjective symptoms and exercise tolerance, which were the inverse of prior findings evaluating TMR as sole therapy (see above).
A 2005 meta-analysis of 7 randomized trials, by Liao and colleagues, involving 1,053 patients concluded, at 1-year follow-up, that TMR produced a significant improvement in angina class but no improvement in survival. (12) In 2008, Campbell et al., conducted a systematic review of TMR and percutaneous TMR (PTMR) for refractory angina pectoris. (13) The authors evaluated 16 RCTs (10 TMR, 6 PTMR) and 13 non-randomized studies (8 TMR, 5 PTMR) and concluded TMR and PTMR were not effective in treating refractory angina and did not improve objective measures of myocardial function (i.e., myocardial perfusion tests and left ventricular ejection fraction) and 12-month survival. While subjective, patient reported outcomes showed some improvement with TMR and PTMR, the review noted improvements in angina symptoms and exercise tolerance were lost or reduced when blinding of treatment occurred. The review found the mortality risks and risk of adverse events raised safety concerns. Additionally, the review also noted most studies were conducted in the United States on male patients, and therefore, there is a lack of evidence on outcomes in wider populations. A 2009 Cochrane review of 7 studies of TMR noted that while improvement in angina was greater in treated patients than in control patients, 1-year mortality was similar between the groups but 30-day mortality was greater in the TMR group. (14) These authors concluded that there was insufficient evidence to determine whether the clinical benefits of TMR outweighed the potential risks.

**Percutaneous Transmyocardial Revascularization (PTMR)**

Although PTMR was designed as a less-invasive alternative to TMR, no studies have directly compared the 2 procedures. The various differences between PTMR and TMR outlined here require that they be considered as distinct entities.

At the time of the original TEC Assessment, (1) no outcome data on PTMR were available, although early observational data suggested that the symptomatic benefit of PTMR approached that seen with TMR. (9) As noted above, in a 2008 systematic review, Campbell et al., concluded PTMR was not an effective treatment for refractory angina pectoris. (13) A 2010 meta-analysis by McGillion and colleagues evaluated 7 RCTs to compare PTMR to maximally-tolerated antianginal therapy management. (15) A total of 1,213 patients with CCS class III-IV refractory angina on optimal medical management were included in the trials analyzed. Exclusion criteria for the trials included recent myocardial infarction (MI), aortic stenosis, mechanical aortic valve, peripheral vascular disease precluding catheter insertion, left ventricular ejection fraction less than 25-30%, and myocardial wall thickness in laser-targeted areas of less than 8-9 mm. All patients randomized to PTMR groups in the trials received low-dose holmium:YAG lasers except for 1 arm of one trial, which used a high-dose holmium:YAG laser. The high-dose laser arm was excluded from the primary analysis. Maximally-tolerated antianginal therapy was not changed in any treatment group across the trials.

Data on 12-month outcomes from 5 of the trials examined were analyzed and demonstrated PTMR significantly reduced angina symptoms by at least 2 CCS classes with a pooled odds ratio (OR) of 2.13 (95% confidence interval [CI]: 1.22 to 3.73) (n=3 studies). PTMR also significantly improved self-reported, health-related quality of life, using the Seattle Angina Questionnaire, in the areas of angina frequency, standardized mean differences (SMD) were 0.29 (95% CI: 0.05 to 0.52), disease perception SMD was 0.37 (95% CI: 0.14 to 0.61), and physical limitations SMD was 0.29 (95% CI: 0.05 to 0.53) (n=2 studies). Significant differences were not found in patient-reported angina stability or treatment satisfaction. Nor were significant differences found in exercise duration or all-cause mortality. Additionally, when a secondary analysis including the high-dose laser group from Leon et
al, was performed, the differences in angina class, exercise duration, and HRQL were no longer significant between treatment and control groups. (16)

This meta-analysis suggests that PTMR may have benefits similar to open TMR, but the conclusions are limited by several factors. Although 7 studies were included in the review, the results for each individual outcome were based on only 2 or 3 studies. The findings of outcome benefits on combined analysis were not robust, as the addition of a third treatment arm from 1 trial eliminated the significant findings. Sensitivity analysis was not performed by study quality, presence of blinding, or the presence of a sham placebo, factors which may have been able to determine whether group differences reported in some of the trials were due to a treatment effect versus a placebo/nonspecific effect. The authors identified a need for further studies to evaluate adverse events, disease-specific mortality, laser dosages, and the underlying mechanisms of PTMR.

The following is an example of 2 published RCTs included in the McGillion et al. meta-analysis above, that compared PTMR to medical management. In the PACIFIC trial, (17) Oesterle et al. compared PTMR (n=110) with medical management (n=111) in patients with refractory angina. Several patients in both the PTMR group (n=10) and the medical management group (n=14) received percutaneous transluminal coronary angioplasty (PTCA), CABG, or TMR within the 12-month follow-up period. When these patients were included in an analysis at 12 months, 46% in the PTMR group improved by at least 2 CCS anginal classes, compared to 11% in the medical management group. However, a subsequent masked assessment of anginal scores revealed that 28% of the improvement was attributable to investigator bias. When the patients who received an additional procedure were excluded, there was still an 82.5-second improvement in exercise duration in the PTMR group over the medical management group. There were more deaths at 12 months in the PTMR group, but the difference was not statistically significant (8 vs. 3, p=0.21).

In the second published RCT, (18) Stone and coworkers studied 141 patients with refractory angina and 1 or more chronic total occlusions (CTOs) in territories with reversible ischemia. This study group was derived from a larger group of patients in whom PTCA of a CTO was attempted. If PTCA was not possible, the patients were immediately randomized to PTMR (n=71) or a sham PTMR procedure followed by medical management (n=70). At 6 months, 49% of the patients assigned to PTMR improved by at least 2 CCS classes versus 37% in the sham group. This difference was not statistically significant (p=0.33). There was a small increase in exercise duration (64 vs. 52 seconds) in the PTMR group over the sham group that was also not statistically significant (p=0.73). There was no difference in mortality at 6 months (8.6% vs. 8.8%, p=NS). The authors concluded that the similar degree of benefit in the sham group compared to the PTMR group suggests that improvement from PTMR may be largely due to a placebo effect.
Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

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NCT: national clinical trial.

\(^{a}\) Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

In 2012, guidelines for stable ischemic heart disease were developed through a collaborative effort of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. These guidelines indicate TMR may be considered as an alternative therapy for refractory angina in patients with stable ischemic heart disease (Class IIb, Level of evidence B: benefit greater than risk, evidence less well-established).

The American College of Cardiology/American Heart Association (ACC/AHA) published guidelines for coronary artery bypass graft surgery (20) and percutaneous artery intervention (21). The most recent 2011 versions of these guidelines both indicate that TMR may be performed as an adjunct to CABG on viable ischemic myocardium that is perfused by arteries that are not amenable to grafting (Class IIb, Level of evidence B: benefit greater than risk, evidence less well-established).

In 2004 (reaffirmed in 2009), the Society of Thoracic Surgeons published recommendations regarding TMR; the recommendations do not distinguish between open and percutaneous approach although it is noted to be less promising than open TMR. (22) Class I recommendations were defined as conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective. There was 1 class I recommendation for TMR as solo therapy as follows:

“Patients with an ejection fraction greater than 0.30 and CCS class III or IV angina that is refractory to maximal medical therapy. These patients should have reversible ischemia of the left ventricular free wall and coronary artery disease corresponding to the regions of myocardial ischemia. In all regions of the myocardium, the coronary disease must not be amendable to CABG or percutaneous transluminal angioplasty either as a result of (1) severe diffuse disease, (2) lack of suitable targets for complete revascularization, or (3) lack of suitable conduits for complete revascularization.”
This recommendation was based on data derived from multiple randomized clinical trials. There were no class I recommendations for TMR combined with CABG. There was 1 class IIa recommendation, which defined conditions for which there is conflicting evidence or a divergence of opinion but for which the weight of evidence or opinion is in favor of usefulness or efficacy. The class IIa recommendation is as follows:

“Patients with angina (Class I-IV) in whom CABG is the standard of care who also have at least one accessible and viable ischemic region with demonstrable coronary artery disease that cannot be bypassed either because of (1) severe diffuse disease, (2) lack of suitable targets for complete revascularization, or (3) lack of suitable conduits for complete revascularization.”

This recommendation was based on data derived from a single randomized trial (23) and data from a Society of Thoracic Surgeons National Cardiac Database. (9) These two class I and class IIa recommendations are essentially consistent with the indications considered medically necessary in this policy for open TMR.

In 2009, the National Institute for Health and Clinical Excellence (NICE) issued guidance on TMR (24) and PTMR (25) based on a 2008 systematic review by Campbell et al, noted above. (13) The NICE guidance on TMR states, “Current evidence on transmyocardial laser revascularization for refractory angina pectoris shows no efficacy, based on objective measurements of myocardial function and survival. Current evidence on safety suggests that the procedure may pose unacceptable risk. Therefore, this procedure should not be used.” The 2009 NICE guidance for PTMR states, “Current evidence on percutaneous laser revascularization for refractory angina pectoris shows no efficacy and suggests that the procedure may pose unacceptable safety risks. Therefore this procedure should not be used”.

U.S. Preventive Services Task Force Recommendations:

TMR and PTMR are not preventive services.

Summary

The evidence for TMR in patients with refractory angina includes several randomized controlled trials (RCTs). Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, hospitalizations, treatment-related mortality, and treatment-related morbidity. The available RCTs have demonstrated that TMR may provide significant improvements in angina symptoms compared with optimal medical management. Although studies have not shown improvements in survival or significant increases in exercise duration, the improvement in symptoms represents a health outcome benefit for patients with class III or IV angina who are not candidates for revascularization, who are refractory to medical management, who have reversible ischemia, and who have a left ventricular ejection fraction greater than 30%. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for TMR as an adjunct to coronary artery bypass graft in patients with documented areas of ischemic myocardium that are not amenable to surgical revascularization includes a number
of RCTs. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, hospitalizations, treatment-related mortality, and treatment-related morbidity. Meta-analyses of these trials have reported an improvement in angina, but no improvement in mortality or other relevant outcomes. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for PTMR as a treatment for patients with refractory angina includes a number of RCTs. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, hospitalizations, treatment-related mortality, and treatment-related morbidity. Although PTMR is less invasive than TMR and some studies have shown improvements in angina symptoms and health-related quality of life, the available evidence is less robust in showing whether PTMR improves net health outcomes. Additionally, there is no U.S. Food and Drug Administration–approved PTMR device available. Therefore, the evidence is insufficient to determine the effect of the technology on health outcomes.

**Medicare National Coverage**

CMS covers TMR 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. (26) 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: an ejection fraction of 25% or greater; have areas of viable ischemic myocardium (as demonstrated by diagnostic study) which are not capable of being revascularized by direct coronary intervention; and 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.

**References**


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December 2015  Update Policy  Policy updated with literature review through July 1, 2015; no references added. Policy statements unchanged.

December 2016  Update Policy  Policy updated with literature review; no references added. Policy statements unchanged.

**Keywords**

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Percutaneous Myocardial Channeling  
Percutaneous Myocardial Revascularization  
Revascularization, Transmyocardial  
Transmyocardial Laser Revascularization (TMLR)  
Transmyocardial Revascularization for the Treatment of Coronary Artery Disease

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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 2, 2016 and is effective January 15, 2017.

_Signature on File_

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