Articles

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

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Summary

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

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

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

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

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Introduction

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

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

Methods

Patients

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

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

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

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

Table 1: **Baseline characteristics of patients**

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

Design and procedures

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

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

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

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

Statistics

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

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

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

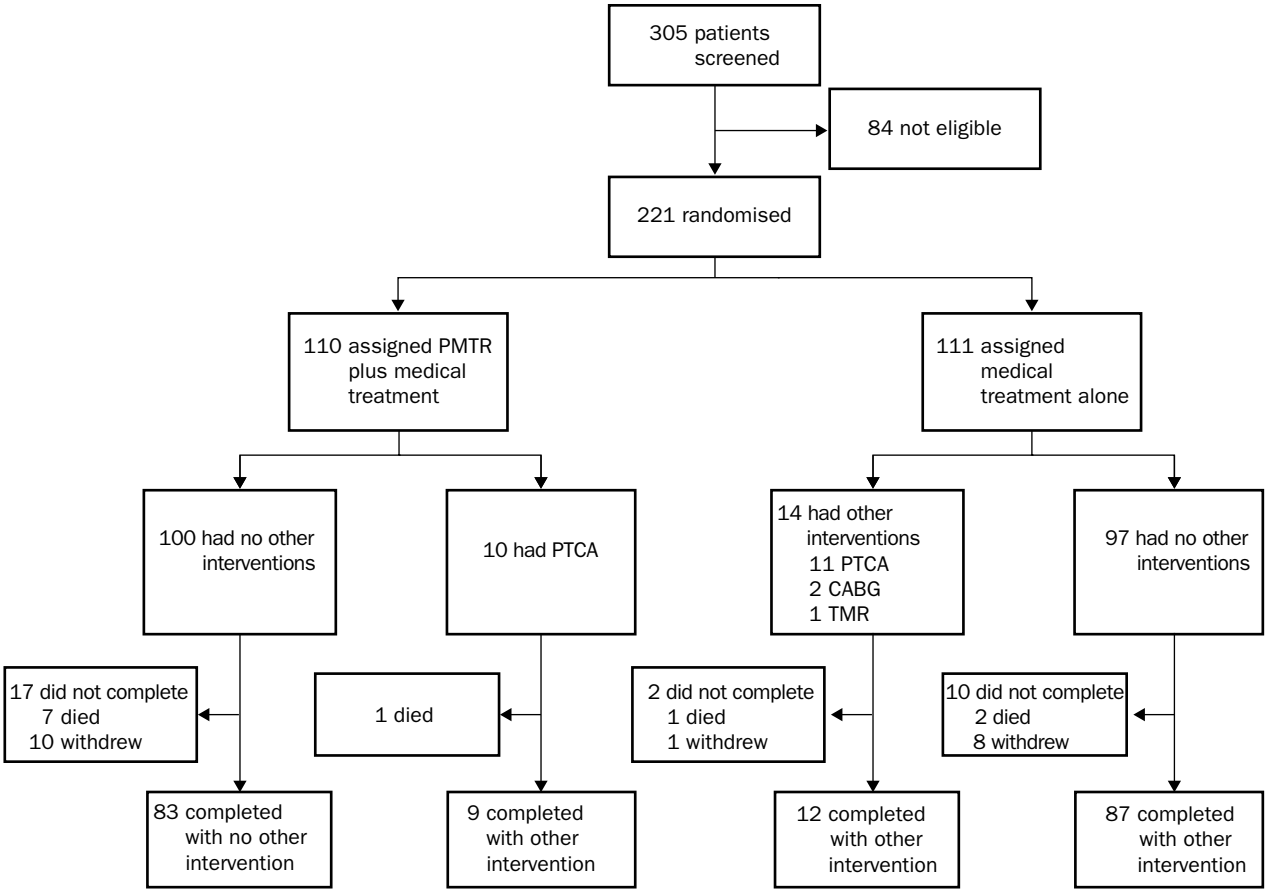


Figure 1: **Trial profile**

Results

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

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

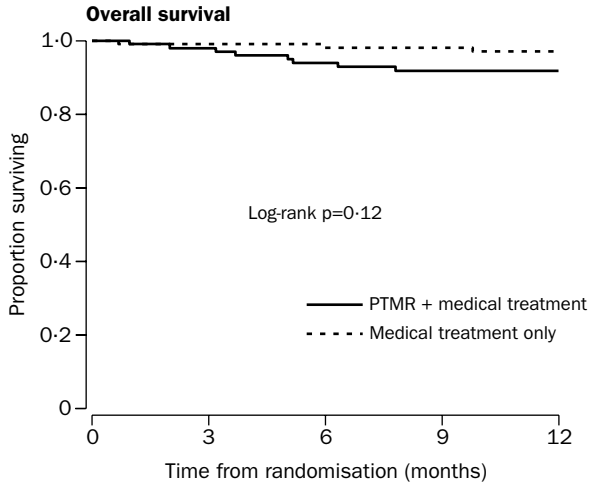
Distributions of age, sex, and results of baseline testing were similar in the two groups, but there were higher proportions of patients with hyperlipidaemia, family history of coronary-artery disease, and previous cardiac interventions in the medically treated group (table 1). However, patients in that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

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

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

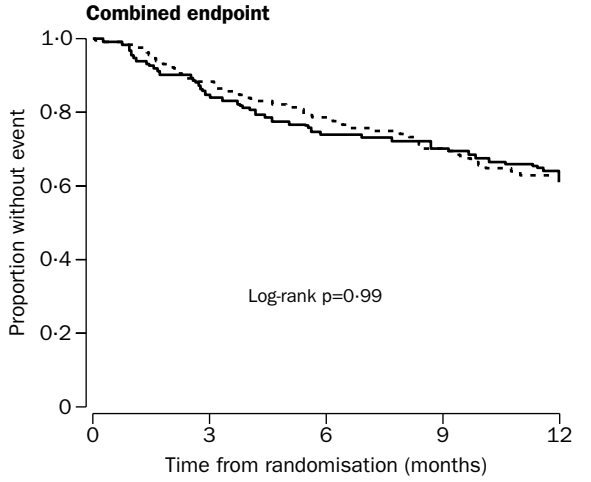
Peak creatine phosphokinase activity (available from 213 patients) averaged 145 IU/L, and the median value was 134 IU/L. The activity of the MB isoenzyme (available from 195 patients) averaged 15·8 IU/L, and the median value was 8·9 IU/L.

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



Number at risk

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



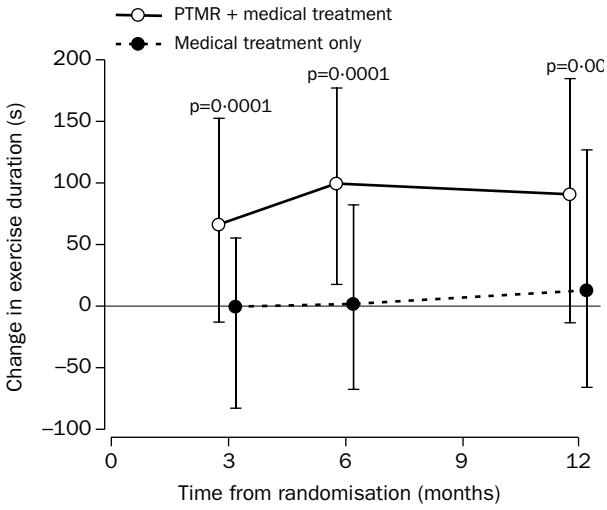
Number at risk

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

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

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

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



Number of patients tested

PTMR	100	91	85
Medical	97	100	90

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

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

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

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

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

Contributors

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

Acknowledgments

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References

1 Mirhoseini M, Shelgikar S, Cayton MM. New concepts in revascularization of the myocardium. *Ann Thorac Surg* 1988; **45:** 415–20.

2 Schofield PM, Sharples LD, Caine N, et al. Transmyocardial laser revascularisation in patients with refractory angina: a randomised controlled trial. *Lancet* 1999; **353:** 519–24.

3 Burkhoff D, Schmidt S, Schulman SP, et al. Transmyocardial laser revascularisation compared with continued medical therapy for treatment of refractory angina pectoris: a prospective randomised trial. *Lancet* 1999; **354:** 885–90.

4 Frazier OH, March RJ, Horvath KA. Transmyocardial revascularization with a carbon dioxide laser in patients with end-stage coronary artery disease. *N Engl J Med* 1999; **341:** 1021–28.

5 Allen KB, Dowling RD, Fudge TL, et al. Comparison of tranmyocardial revascularization with medical therapy in patients with refractory angina. *N Engl J Med* 1999; **341:** 1029–36.

6 Yamamoto N, Kohmoto T, Gu A, DeRosa CM, Smith CR, Burkhoff D. Angiogenesis is enhanced in ischemic canine myocardium by transmyocardial laser revascularization. *J Am Coll Cardiol* 1998; **31:** 1426–33.

7 Kwong KF, Kanellopoulos GK, Nickols JC, et al. Transmyocardial laser treatment denervates canine myocardium. *J Thorac Cardiovasc Surg* 1997; **114:** 883–89.

8 Al-Sheikh T, Allen KB, Straka SP, et al. Cardiac sympathetic denervation after transmyocardial laser revascularization. *Circulation* 1999; **100:** 135–40.

9 Kim CB, Kesten R, Javier M, et al. A percutaneous method of laser transmyocardial revascularization. *Cath Cardiovasc Diagn* 1997; **40:** 223–28.

10 Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol* 1995; **25:** 333–41.

11 Mukherjee D, Bhatt DL, Roe MT, Patel V, Ellis SG. Direct myocardial revascularization and angiogenesis—how many patients might be eligible? *Am J Cardiol* 1999; **84:** 598–600.

12 Kohmoto T, Argenziano M, Yamamoto N, et al. Assessment of transmyocardial perfusion in alligator hearts. *Circulation* 1997; **95:** 1585–91.

13 Kohmoto T, Fisher PE, Gu A, et al. Does blood flow through holmium:YAG transmyocardial laser channels? *Ann Thorac Surg* 1996; **61:** 861–68.

14 Kohmoto T, Fisher PE, Gu A, et al. Physiology, histology and 2-week morphology of acute transmyocardial laser channels made with a CO_2 laser. *Ann Thorac Surg* 1997; **63:** 1275–83.

15 Kohmoto T, Uzun G, Gu A, Zhu SM, Smith CR, Burkhoff D. Blood flow capacity via direct acute myocardial revascularization. *Basic Res Cardiol* 1997; **92:** 45–51.

16 Oesterle SN, Reifart NJ, Meier B, Lauer B, Schuler GC. Initial results of laser-based percutaneous myocardial revascularization for angina pectoris. *Am J Cardiol* 1998; **82:** 659–62.

17 Lauer B, Junghans U, Stahyl F, Kluge R, Oesterle SN, Schuler GC. Catheter-based percutaneous myocardial revascularization in patients with end-stage coronary artery disease. *J Am Coll Cardiol* 1999; **34:** 1663–70.

18 Burkhoff D, Wesley MN, Resar JR, Lansing AM. Factors correlating with risk of mortality following transmyocardial revascularization. *J Am Coll Cardiol* 1999; **34:** 55–61.

19 Nagele H, Stubbe HM, Nienaber C, Rodiger W. Results of transmyocardial laser revascularization in non-revascularizable coronary artery disease after 3 years follow-up. *Eur Heart J* 1998; **19:** 1525–30.

20 Kwong KF, Schuessler RB, Kanellopoulos GK, Saffitz JE, Sundt TM. Nontransmural laser treatment incompletely denervates canine myocardium. *Circulation* 1998; **98** (suppl II): 67–71.