WORKING GROUP ON ACUTE PURCHASING

Transmyocardial Laser Revascularisation for Angina not Controlled by Medication or Amenable to Surgery

April 2000

GUIDANCE NOTE FOR PURCHASERS 00/04
Series Editor: Nick Payne

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of evidence provided, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 11 April 2000 at which this Guidance Note for Purchasers (in a draft form) was considered.

TRANSMYOCARDIAL LASER REVASCULARISATION FOR ANGINA NOT CONTROLLED BY MEDICATION OR AMENABLE TO SURGERY

AUTHORS: Wilson RJ, Slack R, Calvert N, Galinanes M, Gershlick AH. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 2000. Guidance Note for Purchasers: 00/04.

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Dr R J Wilson, Consultant in Public Health, Lincolnshire Health Authority.
Mr M Galinanes, Cardiothoracic Surgeon, Glenfield General Hospital, Leicester.

(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts)

DECISION: The Committee considered that, from the available evidence, transmyocardial laser revascularisation (TMLR) relieves pain at least for some patients with angina that has not responded to medical treatment. More evidence is required to consider medium and long term effects, and to evaluate the clinical effectiveness of this treatment. It was recommended that the procedure should continue to be offered to patients, but only within the context of a clinical trial.

April 2000

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Conflict of Interest None of the authors of this document has any financial interests in the drug or product being evaluated here.

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ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
- provides advice and support to NHS staff on undertaking HSR;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor M Clarke (Leicester); and
Professor H Williams (Nottingham).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (ScHARR).

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Health Authority And Trust Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterTASC, with units in other regions. These are: The Wessex Institute for Health Research and Development and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst
Chairman, Trent Working Group on Acute Purchasing

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SUMMARY

Ischaemic heart disease is the most common cause of death in the UK and angina is a major cause of morbidity. Most patients with angina respond adequately to treatment with medication, angioplasty or bypass grafting. Some patients, however, present with angina that is refractory to such treatments. Transmyocardial laser revascularisation (TMLR) uses laser ablation to create transmural channels in the ischaemic myocardium and, thus, offers a new treatment to patients for whom medication or surgery has not been successful.

There have been few published studies of TMLR. What studies there have been have demonstrated short-term benefit in terms of relief of angina, reduction in hospital admissions for angina, and reduction in the use of cardioactive medications; there is conflicting evidence regarding changes in myocardial perfusion or exercise capacity; there is no improvement in 12 month survival. No studies with long-term follow-up have been published. There is little published data concerning cost-effectiveness: the cost per QALY is estimated to be at least £45,000.

More evidence is required to demonstrate longer-term benefits, and to evaluate cost-effectiveness. TMLR should continue to be offered to patients, but only within the context of clinical trials.

ABBREVIATIONS

AUC	Area Under the Curve
CABG	Coronary Artery Bypass Graft
CCS	Canadian Cardiovascular Society
CS	Case Series
CHD	Coronary Heart Disease
ISTAHC	International Society Technology Assessment in Health Care
LVEF	Left Ventricular Ejection Fraction
MET	Metabolic Equivalent Tests
MM	Medical Management
MSAC	Medicare Services Advisory Committee
PMR	Percutaneous Myocardial Revascularisation
PTCA	Percutaneous Transluminal Coronary Angioplasty
QALM	Quality Adjusted Month
QALY	Quality-adjusted Life Year
RCT	Randomised Controlled Trial
SAQ	Seattle Angina Questionnaire
TMLR	Transmyocardial Laser Revascularisation

1. INTRODUCTORY REMARKS

The basic mechanism of ischaemic cardiac pain (angina pectoris) is a mismatch between the demand for both coronary blood flow and oxygen delivery and the available supply.[1] Typically, it is a gripping or crushing central chest pain or discomfort that may be felt around the whole chest or deep within the chest.[2] The pain may radiate into the neck or face and, rarely, into the teeth, back or abdomen. It is associated with heaviness, paraesthesia or pain in one (usually the left) or both arms. Typically, it is provoked by exercise and is promptly relieved by rest.

Most patients with angina due to coronary artery disease respond adequately to treatment with anti-anginal medication, coronary angioplasty, with or without stenting, or coronary artery bypass surgery.[3] Some patients, however, present with angina that is refractory to such treatments, generally because the coronary disease is diffuse and in the distant part of their coronary circulation, or because they are too unwell to undergo bypass surgery. Transmyocardial laser revascularisation (TMLR) is a new technique that uses laser ablation to create transmural channels in the ischaemic myocardium. Animal studies have shown improvements in mortality, decreases in infarct size, and preservation of contractile function. Early results of TMLR in human beings, sometimes used in combination with coronary artery bypass surgery, were encouraging.

Early publications were largely favourable.[4-8] However, these studies were all case series. In 1999, there have been four randomised controlled studies published.[3,9-11] The studies by Burkhoff, Allen and Frazier showed largely favourable results, in contrast to the study by Schofield, which concluded that the technique could not be recommended. Accompanying editorials in The Lancet[12] and The New England Journal of Medicine[13] have also recommended caution.

The purpose of this Guidance Note is to review the evidence of effectiveness for the use of TMLR in patients with angina not controlled by medication or amenable to surgery. In addition, an economic analysis of this treatment is described.

2. DESCRIPTION OF UNDERLYING DISEASE

2.1 CORONARY HEART DISEASE

Coronary heart disease (CHD) is the most common cause of death in the UK with 110,000 deaths in England in 1998. In nearly all cases, coronary artery disease is due to atherosclerotic changes;[1] other causes include syphilis, various forms of arteritis, coronary embolism, and connective tissue disorders.

There are numerous classifications of coronary heart disease by type. The following has been suggested:[1]

- asymptomatic coronary heart disease, manifested by induced myocardial ischaemia;
- sudden death;
- stable angina pectoris; variant (Prinzmetal's) angina; coronary spasm; 'silent ischaemia';
- unstable angina pectoris;
- acute myocardial infarction;
- cardiac failure;
- cardiac arrythmias or atrioventricular conduction defects.

There are marked variations in mortality rates across the country:[14]

- Geography. Mortality is higher in the north of England;
- Social Class. There is a consistent trend in mortality rates. The lowest rates are in Social Class I and the highest in Social Class V;
- Ethnicity. Mortality varies between ethnic groups. Mortality from CHD is higher in people from the Indian subcontinent.

The risk factors for CHD are well documented:[14]

- Smoking - Estimated to account for up to 18% of CHD deaths. For those who smoke, stopping smoking is the single most effective means of reducing risk of CHD;
- Hypertension;
- Raised plasma cholesterol;
- Inadequate physical activity;
- Excessive alcohol consumption;

- Obesity;
- Salt intake;
- Diabetes.

The Welsh Heart Survey and the British Regional Heart Study estimated that 25% of middle aged men showed some evidence of heart disease, amounting to 1.74 million people under the age of 65 in England and Wales.[15]

Analysis of information derived from general practitioner medical records held on the General Practice Research Database allows an estimate of the prevalence of treated coronary heart disease per 1,000 patients.[16] For males in 1996, the age standardised prevalence of treated coronary heart disease was 34.7 per 1,000 patients. For females in 1996, the age standardised prevalence of treated coronary heart disease was 20.8 per 1,000 patients.

In the practices participating in the Trent Focus (a network of general practices willing to collaborate in research to facilitate high quality, co-ordinated primary health care-based research in Trent) the mean prevalence of ischaemic heart disease in practices with complete data was 3.84%.[17] By comparison, for practices participating in the Collection of Health Data from General Practice project, the mean prevalence was 2.97%.

Table 1 Estimates for Ischaemic Heart Disease for a 'Typical' Primary Care Group of 100,000 Population and a Health Authority of 500,000

	PCG	HA
Ischaemic heart disease (Prevalence)	2,970[a] - 3,840[b]	14,850[a] - 19,200[b]
Angina (Incidence)	83[c]	415[c]

[a] Mean prevalence of 2.97%.

[b] Mean prevalence of 3.84%.

[c] Crude incidence of 8.3 per 10,000 per annum (see text above for references).

2.2 ANGINA

The primary cause of angina is insufficient supply of oxygen to the myocardium. This is usually provoked by exertion but can occur at rest; severity and prognosis are variable. Several studies have attempted to estimate the incidence and prevalence of angina. These studies are quite variable in their estimates, reflecting their different study populations. The annual consultation rate within general practice is around 70 per 10,000 patients[18] with a male to female ratio of 4 to 3. The same authors estimate the five-year prognosis as follows:

- death 20%
- no symptoms or controlled without medication 15%
- symptoms well controlled with medication 35%
- moderate control with medication 20%
- severe symptoms 10%

The Fourth National General Practice Morbidity Study[19] found that the number of patients who consulted their GP at least once during the year for angina was 130 and 98 per 10,000 person years at risk for men and women respectively. This represents a 60-69% increase since the previous GP Morbidity Survey carried out in 1981. The survey estimated that the incidence of new and first-time episodes of angina was 55 and 49 per 10,000 person years at risk in men and women respectively. Gandhi et al.[20] found an overall crude incidence of 8.3 per 10,000 per annum in patients aged 31-70 years of age.

3. CURRENT SERVICE PROVISION

3.1 MEDICAL TREATMENT

The investigations and treatments that people with stable angina should usually be offered unless contraindicated are:[21]

Aetiological investigations:

- Haemoglobin, 12 lead resting ECG.

Estimation of risk:

- Plasma glucose, serum cholesterol;
- Assessment of severity of myocardial ischaemia (e.g. Exercise ECG, thallium scan).

Treatment to relieve symptoms:

- Sub-lingual nitrates for immediate symptom control;
- Background beta blockers and/or nitrates and/or calcium antagonists.

Treatment to reduce cardiovascular risk:

- Advice about how to stop smoking including advice about the use of nicotine replacement therapy;
- Information about other modifiable risk factors and personalised advice about how they can be reduced (this includes advice about physical activity, diet, alcohol consumption, weight and diabetes);
- Advice and treatment to maintain blood pressure below 140/85 mmHg;
- Low dose aspirin (75mg daily);
- Statins and dietry advice to lower serum cholesterol concentrations *either* to less than 5mmol/l (LDL-C to below 3mmol) *or* by 30% (whichever is greater);
- Education about symptoms of heart attack and, should they develop, instruction to seek help rapidly by calling '999'.

When angina occurs frequently or with only modest exertion, regular prophylactic therapy should be advised. This consists of nitrates, beta adrenergic blocking drugs or calcium antagonists.[2] Aspirin, and, where appropriate, statin therapy to lower cholesterol should be given.

Information is available on the number of prescriptions for each type of medication. However, it is not possible to identify from this information the indication for the prescription. In 1996, an age standardised rate of 36.2 per 1,000 male patients, and 43.5 per 1,000 female patients were prescribed beta adrenoceptor blocking drugs. The comparable rate for nitrates and calcium channel blocking drugs in 1996 was 43.7 per 1,000 male patients, and 35.8 per 1,000 female patients.

A recent review of treatments for chronic stable angina[22] found that:

- few studies exist of the long-term effectiveness of medical treatment with little evidence of large differences between different classes of drug;
- there is little evidence on patients' quality of life;
- no UK cost or cost-effectiveness studies were identified.

3.2 CORONARY ANGIOPLASTY

This is a technique of dilating coronary atheromatous obstructions by inflating a balloon against the obstruction.[2] The balloon, which is mounted on the tip of a very thin catheter, is inserted through the obstruction using X-ray fluoroscopy, and it is then inflated with dilute contrast material. Multiple inflations of the balloon using a pressure of several atmospheres will squash and crush the atheroma and relieve the obstruction. This technique is widely applied for the treatment of angina due to isolated, proximal, non-calcified, atheromatous plaques, usually in patients with a relatively short history of coronary ischaemia. Multiple lesions may be treated and repeat procedures can be undertaken.

Evidence supports percutaneous transluminal coronary angioplasty (PTCA) in terms of relief of angina, but evidence on myocardial infarction rates is conflicting.[22] Clinical benefit is apparently reflected in improved health-related quality of life, although information on long-term effects of revascularisation is lacking.

3.3 CORONARY ARTERY BYPASS GRAFT

Surgical treatment of angina is considered when medical management is no longer sufficient, and for severe disease. A vein (usually saphenous) or internal mammary artery is used to bypass the areas of occlusion. Coronary artery bypass grafts (CABG)s have mortality benefits for up to five years, and possibly longer, compared with medical therapy,

particularly in patients with a greater extent of disease.[22] CABGs are most cost-effective in patients with severe angina, left main vessel disease and multi-vessel disease.

By international standards, the UK has high rates of CHD, but low rates of coronary artery revascularisation.[23,24] There are marked geographical, gender and racial variations in revascularisation rates which are not closely correlated with measures of the level of heart disease in the community.[25-27] The National Service Framework for Coronary Heart Disease recommends a substantial increase in revascularisation rates and a renewed effort to reduce inequities in treatment rates.[21]

4. DESCRIPTION OF NEW INTERVENTION

In the reptilian heart, the myocardium has a sinusoidal structure and the myocardium is perfused by passive diffusion of oxygenated blood. This concept stimulated interest in a technique that potentially allowed oxygenation of human myocardium by the same means. In TMLR the heart is exposed through a left anterolateral thoracotomy. A laser (carbon dioxide or Holmium) is then applied to the epicardial surface of the left ventricle, and sufficient energy applied to create small channels, from the epicardial to endocardial surface, in areas of myocardium previously identified as ischaemic.[13] The laser is synchronised with the heartbeat and automatically fires when the ventricle is filled with blood.[28] Remaining laser energy is absorbed by the blood, preventing damage to other heart tissue. Typically, 10 to 50 channels are created.

Three possible mechanisms have been suggested, but the actual mode of action is unclear:

- Direct revascularisation i.e. the laser created channels remain patent and oxygen diffuses directly to the myocardium;
- Stimulation of angiogenesis i.e. new vessel formation;
- Myocardial denervation.

Transmyocardial laser revascularisation is suggested for the treatment of patients with Class III or Class IV stable angina not amenable to medical treatment and conventional coronary revascularisation, according to the Canadian Cardiovascular Society (CCS) classification system for angina.[28]

Table 2 The Canadian Cardiovascular Society Grading of Angina.

Class I	Ordinary physical activity does not cause angina. (Strenuous physical activity provokes angina).
Class II	Slight limitations of ordinary physical activity. (Climbing more than one flight of stairs or walking uphill provokes angina).
Class III	Marked limitation of ordinary physical activity. (Walking on the level or climbing one flight of stairs provokes angina).
Class IV	Inability to carry on any physical activity. (Angina may be present at rest).

Note: Limitations to normal activity are: class I - none; class II - slight; class III - marked; class IV - severe.

Most patients treated in clinical trials have already received at least one bypass graft and are at high risk of re-operation. For medical reasons, these patients are not expected to benefit from angioplasty. It has been estimated that 80,000 Americans qualify for TMLR annually.[28]

4.1 POTENTIAL COST (CANADIAN CO-ORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT, 1998)

The Heart Laser™ (PLC Medical Systems, Inc.) sells for US $400,000; the disposables for each procedure sell for US $1,500. The operation takes approximately two hours to complete and does not require a heart-lung machine. The average hospital stay following TMLR ranges from five to seven days and is generally less than the recovery time following CABG.

4.2 PERCUTANEOUS MYOCARDIAL REVASCULARISATION

Percutaneous myocardial revascularisation (PMR) is also a method of treatment for patients with refractory angina. In comparison with TMLR, it is a less invasive procedure. In the UK a trial is currently being undertaken at Papworth Hospital where patients are being randomised to either PMR or medical therapy. Initial findings at 12 months indicate that for PMR patients mean exercise time on the treadmill increased by 79 seconds, compared to an increase of 35 seconds for the medical therapy group ($p=0.028$). In comparison with TMLR, there is evidence to suggest that there are fewer post-operative complications, and that the mortality rate is lower, for patients receiving PMR (Tait - Personal Communication 2000).

5. METHODS

The medical literature was searched in order to identify relevant studies for inclusion in this paper. Searches on EmBASE, MEDLINE, and Cochrane Library were undertaken using the following search strategy.

- #1 transmyocardial laser revascularisation;
- #2 laser* and revasculari* and angina*;
- #3 #1 or #2 (169 records);
- #4 #1 or #2 (86 records).

All databases were searched from 1990 onwards. Papers identified in this search were supplemented with recently published literature from known journals. Papers retained for inclusion in this study were required to be papers reporting the results of randomised controlled trials (RCT)s or case series studies. If papers reporting findings produced results in an interim paper, this was discarded in situations where a paper reporting the final findings of the study was available.

6. RESULTS

6.1 QUANTITY AND QUALITY OF RESEARCH AVAILABLE

6.1.1. Quantity and Type of Evidence Available

A total of ten studies were identified, two of which were rejected because they had preliminary results of patients who were included in later studies,[6,29] leaving eight studies for the review (see Table 3). In 1999 four RCTs comparing this procedure to the medical treatment of angina, were published, and a further four case series have described the results of the procedure.

Table 3 Summary of Studies Included in the Review

Authors	Setting	Study	Patient Groups
Allen et al. (1999)[10]	USA	RCT	Transmyocardial revascularisation followed by continued medical therapy (n=132) vs medical therapy alone (n=143).
Burkhoff et al. (1999)[9]	USA	RCT	Transmyocardial revascularisation and continued medication (n=92) vs medical therapy alone (n=90).
Frazier et al. (1999)[11]	USA	RCT	Transmyocardial revascularisation (n=91) vs continued medical treatment (n=101).
Schofield et al. (1999)[3]	UK	RCT	Transmyocardial revascularisation plus normal medication (n=94) vs continued medication alone (n=94).
Cooley et al. (1996)[8]	USA	CS	Transmyocardial revascularisation (n=21).
Horvath et al. (1997)[5]	USA	CS	Transmyocardial revascularisation (n=200).
Vincent et al. (1997)[7]	Switzerland	CS	Transmyocardial revascularisation (n=268).
Nagele et al. (1998)[4]	Germany	CS	Transmyocardial revascularisation (n=60).

Note: CS = Case series

Some papers include patients who have received TMLR in addition to CABG or PTCA. Due to the small numbers of such patients that have been reported, the results from this sub-group of patients are not described further in this analysis.

The quality of the published studies is variable with several problems when attempting to compare studies:

- Inclusion criteria vary between studies. In particular, the degree of severity of angina - in most studies patients were predominantly Class IV on the CCS classification of angina, but some studies included patients with Class III. No study reported results separately by level of severity at baseline.

- Some studies accepted patients with a left ventricular ejection fraction (LVEF) as low as 20% whereas other studies had a higher threshold. This difference is particularly significant when comparing mortality rates as there is a clear correlation between very low LVEF and death.

- Some studies did not state the number of patients who had been excluded from further treatment having been referred for inclusion. Those studies that did report the number of exclusions typically excluded half the patients referred to them.

- Follow-up was brief. Only one study reported results at three years whilst the other studies typically reported at 12 months follow-up.

- Reporting of methods was variable. For example, two of the RCTs did not report if statistical power had been estimated.[10,11]

- The numbers of patients were small in most studies. This was aggravated by the fact that two of the RCTs permitted patients originally assigned to receive medical treatment to then have TMLR if their angina remained severe.[10,11]

6.1.2 Outcome Measures

All studies used the CCS grading of angina (see Table 2). Relief of angina is typically defined as an improvement of at least two classes on this scale from baseline.

6.2 EVIDENCE OF EFFECTIVENESS

Despite the fact that there have only been 10 published studies, a large number of different outcome measures have been used: These are tabulated in Table 4, where a 'v' denotes that the outcome was used in the study.

Table 4 Outcome Measures Used in the Studies

	Study Number (see footnote)							
Outcome Measure	1	2	3	4	5	6	7	8
Survival	v	v	v	v	v	v	v	v
Mortality	v	v	v	v	v	v	v	v
Angina relief	v	v	v	v	v	v	v	
Hospital admissions	v	v	v	v		v		
Use of cardiac medications	v	v	v	v		v		v
Myocardial perfusion	v	v	v	v	v	v	v	v
LVEF		v		v	v		v	
Exercise capacity	v	v		v	v		v	
Echocardiography		v			v		v	
Stress test		v					v	
Chest pain				v				
Positron tomography						v		
SF-36			v	v*				
Euroqol				v*				
Seattle Angina Questionnaire		v	v					
Duke Activity Status Index	v							
Unspecified quality of life							v	

Study: 1 - Allen et al.; 2 - Burkhoff et al.; 3 - Frazier et al.; 4 - Schofield et al.; 5 - Cooley et al.; 6 - Horvath et al.; 7 - Vincent et al.; 8 - Nagele et al.

Note. * Used, but not reported in this paper for the study.

6.2.1 Outcomes Related to Mortality

By definition, patients receiving this treatment are very sick and, thus, are expected to have a limited life expectancy. This emphasises the need to have a good control group in any study. Some studies included sicker patients than others (i.e. more severe disease) and, thus, it is difficult to compare mortality rates across different studies. No studies demonstrated improvements in survival 12 months after TMLR.

Peri-operative mortality rates (defined as deaths within 30 days of procedure) varied markedly across studies: this may reflect different inclusion criteria or could be due to better operative and anaesthetic techniques, perhaps related to greater experience with the procedure.

The results presented in Table 5 indicate that there is no statistical difference in mortality between the two treatment methods, with no significance indicated in the four RCTs. The level of significance is so low that combining the studies into a meta analysis would be unlikely to produce a significant result.

6.2.2 Outcomes Related to Relief of Angina

If relief of angina is defined as a reduction of at least two classes in the CCS score, then there is good evidence to suggest that TMLR is effective at relieving the pain of angina. All four RCTs showed a significant advantage comparing TMLR to medical treatment.

The rate of hospital admissions for angina is also reduced by TMLR. However, only one study[3] reports the total number of hospital admissions, including those due to complications from the procedure: they found no difference between the two groups in the total number of hospital admissions.

Use of cardioactive medications is also reduced by TMLR.

Table 5 12 Month Survival Following TMLR or Medical Treatment & Number and Proportion of Deaths from TMLR within 30 days of Procedure

	12 Month Survival		Proportion of Deaths in 30 Days	
Study	**Proportion Alive at 12 Months**	**Sig**	**Number of Deaths**	**%**
Frazier et al.[11]	TMLR - 85% (of 91 patients) Medical - 79% (of 41 patients)	NS (p=0.5)	3 (of 91 patients) 2 (of 41 patients)	3.3% 4.9%
Burkhoff et al.[9]	TMLR - 95% (of 92 patients) Medical - 90% (of 90 patients)	NS	1 (of 92 patients) 0 (of 90 patients)	1.1% 0%
Allen et al.[10]	TMLR - 84% (of 132 patients) Medical - 89% (of 143 patients)	NS (p=0.2)	7 (of 132 patients) 2 (of 97 Patients)	0.8% 2.1%
Schofield et al.[3]	TMLR - 89% (of 94 patients) Medical - 96% (of 94 patients)	NS (p=0.1)	5 (of 94 patients) Not Stated	5.3% -
Vincent et al.[7]	TMLR – 90.5% (of 124 patients)	N/A	1 (of 124 patients)	0.8%
Cooley et al.[8]	TMLR – 76.2% (of 21 patients)	N/A	4 (of 21 patients)	19.0%
Nagele et al.[4]	TMLR – 76.7% (of 60 patients)	N/A	7 (of 60 patients)	11.7%
Horvath et al.[5]	TMLR – 82.5% (of 200 patients (at 10 months)	N/A	18 (of 200 patients)	9.0%

Table 6 Relief of Angina at 12 Months (Defined as Reduction in CCS Score of at Least 2 Classes), Rate of Hospital Admission for Angina within 12 Months and Use of Medications

Study	Proportion with Relief of Angina		Hospital Admissions	Use of Medications
Frazier et al.[11]	- TMLR - Medical including crossover* - Medical without crossover*	- 72% (of 61 patients) - 43% (of 54 patients) - 13% (of 20 patients) p<0.001	2% of TMLR patients admitted with unstable angina. 69% of medical patients admitted with unstable angina. p<0.001	Use of cardioactive medications decreased or remained unchanged in 83% of the patients in whom TMLR was successful. Use of medications increased or remained unchanged in 86% of the patients assigned to medical treatment.
Burkhoff et al.[9]	- TMLR - Medical	- 61% (of 77 patients) - 11% (of 73 patients) Significance level not stated	37 admissions due to unstable angina in TMR group (92 patients). 69 admissions due to unstable angina in medical group.	States 'little change in the overall pattern of medications during the study' (no further details given).
Allen et al.[10]	- TMLR - Medical including crossover* - Medical without crossover*	- 76% (of 76 patients) - 78% (of 37 patients) - 32% (of 50 patients) p<0.001	39% of TMLR patients had cardiac related hospitalisations. 67% of medical patients had cardiac related hospitalisations. p<0.001	Calcium channel blockers reduced in the TMLR group (p=0.002). Beta blockers reduced or discontinued in the TMLR group (p=0.02). Nitrates reduced in the TMLR group (p=0.12).
Schofield et al.[3]	- TMLR - Medical	- 25% (of 74 patients) - 4% (of 78 patients) p<0.001	TMLR patients had average 0.5 admissions with angina. Medical patients had average 0.8 admissions with angina. p=0.015	Reduced use of calcium antagnosists in the TMLR group (p<0.001). Reduced use of nitrates in the TMLR group (p=0.025).
Vincent et al.[7]	Not possible to calculate from data in paper		Not stated.	N/A
Cooley et al.[8]	- TMLR	- 85% (of 13 patients)	Not stated.	N/A
Nagele et al.[4]	Not possible to calculate from data in paper		7% admitted with unstable angina.	N/A
Horvath et al.[5]	- TMLR	- 74% (of 95 patients)	In the year prior to TMLR, patients averaged 2.5 admissions for angina. In the year following TMLR there was an average of 0.4 admissions. P<0.001	12 months after TMLR, 56% had reduced their cardioactive medications whilst 19% had increased use.

*These studies allowed patients who had been assigned to medical treatment to receive TMLR if severe angina persisted. The results of these studies are presented separately for those who received TMLR (crossover) and those who did not.

6.2.3 Outcomes Related to Functional Capacity of the Heart

One RCT,[11] and one other study[5] demonstrated objective improvements in myocardial perfusion; the three other RCTs showed no improvement. The significance of this is that the most favoured mechanism of action for TMLR is that it stimulates new vessel formation; if this is the mechanism of action then one would expect an improvement in myocardial perfusion.

LVEF was not measured in two of the RCTs and two of the case series. Only one study[7] showed an improvement.

Most studies show an increase in exercise capacity although one of the RCTs[3] did not.

Table 7 Myocardial Perfusion, Left Ventricular Ejection Fraction and Exercise Capacity

Study	Myocardial Perfusion Results	LVEF	Exercise Capacity
Frazier et al.[11]	Myocardial perfusion (calculated as the number of defects at baseline minus the number of defects at follow-up, divided by the number of defects at baseline) improved by 20% in the TMLR group and worsened by 27% in the medical treatment group (p=0.002).	Not measured at follow-up.	N/A
Burkhoff et al.[9]	At 12 months the median proportion of the myocardium affected by ischaemia was 11.5% in the TMLR group and 12% in the medication only group (not statistically significant).	LVEF did not change significantly in the medication only group from baseline to 3 months (median change 0%). In the TMLR group, the median change from baseline to 3 months was a decrease of 3%.	Exercise tolerance test. TMLR - median time (baseline) - 364 sec (range 105 - 981) - median time (12 months) - 429 sec medical management (MM) - median time (baseline) - 381 sec (range 89 - 747) - median time (12 months) - 335 sec Median difference 111 sec, p<0.0001 between groups.
Allen et al.[10]	No significant differences with respect to changes in ischaemia, defects in perfusion at rest or delayed effects. No correlation between improvement in angina and the results of thallium scanning.	Not measured at follow-up.	Treadmill test (results expressed as metabolic equivalents (MET)). TMLR - MET of 5.0, MM - MET of 3.9 (p=0.05).

Schofield et al.[3]	In both TMLR and medical groups the number of sites with reversible ischaemia decreased and the number with irreversible ischaemia increased. The overall number of sites with reversible ischaemia did not differ significantly between groups, but there is a small excess of sites with irreversible ischaemia among TMLR patients.	Mean LVEF was 49% at baseline in the medical group and 48% in the TMLR group. At 12 months, the mean LVEF was 48% in the medical group and 46% in the TMLR group.	Treadmill exercise time. At 12 months the mean improvement in exercise time in the TMLR group was 40 seconds longer than in the medical group (NB: no baseline values stated).
Vincent et al.[7]	At 12 months, 27% had better perfusion, 45% had identical, and 18% worse.	Compared to baseline, LVEF was better or identical in 78% of patients at 12 months.	Ergometry stress test. At 12 months, 64% of TMLR patients had a better result, 14% identical, 21% worse.
Cooley et al.[8]	Average perfusion of the laser treated regions increased from 45% of normal at baseline to 51% of normal at 12 months; the perfusion of the non-lasered segments decreased from 73% of normal at baseline to 70% of normal at 12 months (differences not statistically significant).	Mean LVEF was 48% at baseline and 50% at 12 months.	Treadmill test. Mean time at baseline 4.3 mins; at 12 months mean time had increased to 10.0 mins.
Nagele et al.[4]	Increase in moribund and decrease in normal cardiac segments at 12 months ($p<0.05$) i.e. worsening of perfusion.	Not measured at follow-up.	N/A

Horvath et al.[5]	Treated area showed a statistically significant decrease in the number of segments with reversible perfusion defects, and no change in the number with fixed defects, at 12 months. Untreated area showed no significant change in either fixed or reversible defects.	Not measured at follow-up.	N/A

6.2.4 Outcomes Related to Quality of life

This is difficult to assess as only four studies included an assessment of quality of life; three different assessment tools were used and one study did not state which tool was used. However, all four studies showed an improvement in the quality of life of patients following TMLR.

Table 8 Quality of Life

Study	Quality of Life Data
Frazier et al.[11]	Used SF36 and Seattle Angina Questionnaire (SAQ). Using the SF36, the TMLR group improved significantly more (38% improvement) than the medical group (6% improvement) at 3 months, and this difference was also significant at 6 and 12 months ($p<0.001$ at 3 month, $p=0.01$ at 6 month and $p<0.001$ at 12 month). For each of the 15 components of the SAQ the TMLR group scored significantly better (no details given).
Burkhoff et al.[9]	Used SAQ At 3, 6 and 12 months, scores of each quality of life index in the SAQ were significantly better in the TMLR group than in the medication only group (no details given in the text).
Allen et al.[10]	Used Duke Activity Status Index (a scale of 0 to 58, higher scores are better). At 12 months, the TMLR group had a mean score of 21 compared to 12 for the medical group ($p=0.003$).
Schofield et al.[3]	Collected quality of life data, but not reported in this paper.
Vincent et al.[7]	67% reported an improvement, and 21% steady state, in their well-being. No details given of assessment tool used.
Cooley et al.[8]	N/A
Nagele et al.[4]	N/A
Horvath et al.[5]	N/A

6.3 ECONOMIC ANALYSIS

There are no known published papers which report the costs or cost-effectiveness of the TMLR treatment, though a recent report by the Medicare Services Advisory Committee (MSAC)[30] contains cost information and a cost-effectiveness analysis. None of the studies assessed or reported within this Guidance Note reports the costs of the intervention, and only a small number of the papers make any reference to the quality of life benefits resulting from the intervention.

Papers on the costs and health-related quality of life information from the Schofield et al.[3] trial are forthcoming, but are not yet available to use in the analysis presented here. However, it is possible to use utility results from this study which were presented as part of a recent conference abstract.

In view of the lack of published research evidence on the cost-effectiveness of TMLR, this paper attempts to estimate the costs and benefits of TMLR using a spreadsheet modelling approach. The modelling assumptions are made using evidence of benefits from the Schofield et al.[3] study and costing information presented in the MSAC report.[30]

It is likely that further information on both the benefits and costs will become available in due course, but it was not available in time for this document.

6.3.1 Estimation of Net Benefits

Health related quality of life for TMLR vs medical management (MM) was considered in the Schofield et al.[3] study, but was not reported in their paper. Additional information reporting this analysis in terms of EuroQol utility scores was presented in abstracts submitted to the International Society Technology Assessment in Health Care (ISTAHC) conference held in Rotterdam in 1999. Further papers reporting this analysis are in preparation, but are not yet available for consideration here.

The ISTAHC abstract EuroQol utility scores have been used to estimate Quality-Adjusted Months (QALM)s and hence Quality-Adjusted Life Years (QALY)s for each of the treatment options. The area under the curve (AUC) was modelled using a simple spreadsheet approach in order to estimate QALMs (see Table 9).

The total number of QALMs, and hence QALYs, for all the individuals in each of the treatment arms in the Schofield et al.[3] trial was estimated. This allows a calculation of the average values across individuals and, thus, the total QALMs attributed to the numbers of patients remaining in the study at differing time points as referenced by the survival analysis reported by Schofield et al.[3] It should be stressed that uncertainty exists in interpreting these utility values and also the numbers of survivors in the trial as the actual number of survivors is unknown.

Table 9 EuroQol Utility Scores

	EuroQol utility value				
	Base	3 months	1 year*	2 year*	3 year
TMLR	0.44	0.54	0.52	0.50	0.48
MM	0.43	0.44	0.46	0.50	0.53

Data contained in an abstract submitted to the ISTAHC conference.

* Extrapolated values (linear).

6.3.2 Estimation of Net Costs

The MSAC report disaggregated costs during the first year; these gave the procedure costs for TMLR as Aus $10,748 (£4,299 assuming £1 = Aus $2.50), costs for TMLR equipment as Aus $5,800 (£2,320), costs or hospitalisations for unstable angina as Aus $60 (£24), with the cost for complications as Aus $930 (£372). Comparable costs for medical management were Aus $4,102 (£1,641) for hospitalisations for unstable angina, and Aus $907 (£363) for complications. Thus, year 1 total costs are estimated at Aus $17,539 (£7,016) for TMLR and Aus $5,009 (£2,004) for medical management. Costs for subsequent years were given as Aus $712 (£285) for TMLR and Aus $5,009 (£2,004) for medical management. A significant difference between these two costs is the cost of hospitalisations for unstable angina. These hospitalisation costs were derived by applying a cost per episode of Aus $2,994 to assumed treatment rates of 0.02 episodes per patient per annum for TMLR and 1.37 episodes per patient per annum for medical management. These assumed unstable angina health benefits of TMLR have been heavily criticised by MSAC and are said to be biased in favour of TMLR. Bearing this in mind, the costs for subsequent years are then given as Aus $712 (£285) for TMLR and Aus $5,009 (£2,004) for medical management. The implication of these costing assumptions is that during year 4, the total cost of TMLR will be overtaken by that for medical management. This outcome is heavily dependent on the validity of the hospitalisation assumptions used.

Due to differences in treatment patterns, for example, costs in Australia are unlikely to be the same as in the UK. For the purposes of the modelling reported in the following section these, however, are the assumptions that have been used.

6.3.3 Estimation of Cost-effectiveness and/or Cost-utility

The MSAC report undertook a cost-effectiveness analysis to a three year duration. The report found that the incremental cost of TMLR to MM was Aus $12,530 (£5,012) in the first year with savings occurring in the second and third years if the response to TMLR is sustained through symptom relief. Additional incremental cost-effectiveness ratios were calculated within the report. The ratio for the first year after TMLR per extra patient free of unstable angina was Aus $18,159 (£7,264) and per extra patient free of disabling angina was Aus $21,237 (£8,495).

The MSAC report highlights the fact that the projected savings for both the second and third years, post TMLR, are based upon the assumption that the treatment effect is sustained and that the chance of having disabling angina remains unchanged in both the TMLR and MM groups. This assumption remains central to the claimed cost savings of TMLR, but it also lacks substantiated evidence. The report concludes that further evidence on the long-term effectiveness and cost-effectiveness of TMLR would be required in order to support these claims further.[30]

In order to model the cost-effectiveness of TMLR, in this paper the utility values from the UK study have been combined with the costs detailed within the MSAC report. Once again, it should be reiterated that these figures are subject to considerable uncertainty and should be up-dated by further findings from the UK trial as soon as they become available.

However, bearing the above assumptions in mind, the incremental costs per QALY for the first three years are reported in Table 10.

Table 10 Incremental Costs per QALY (costs and benefits discounted at 6%)

	Incremental Cost per QALY (based over three different time periods)		
	Year 1	Year 2	Year 3
TMLR vs MM	£89,092	£61,497	£45,815

Clearly, these figures suggest that the costs of TMLR are expensive relative to the reported QALY gain. Extrapolation further into the future suggests that these ratios will decrease moderately, but this assumes that the years following laser treatment require only minimal costs and no additional laser treatment and that the health benefits remain.

7. EQUITY ISSUES

It is widely acknowledged that there are distinct national and local variations in the rates of treatment for angina. Utilisation will be influenced by a variety of factors. Firstly, there is a requirement to consider need. The epidemiology of the disease dictates that this will vary from location to location, even when differences in age and population structure are adjusted for. Secondly, demand will vary and will be dependent upon factors such as patient consultation thresholds, GP referral thresholds and clinician referral and intervention thresholds. Finally, supply may be important within the context of this procedure, because the location of the equipment to undertake the procedure will be restricted to specialist centres.

Given that there is good evidence that the inverse care law applies in relation to the provision of interventional cardiology,[26] it is essential that any additional investment in revascularisation treatments is targeted towards those in greatest need.

8. OPTIONS FOR PURCHASERS/COMMISSIONERS

Given that the published evidence for the effectiveness of this procedure is limited, it is not possible to make a definitive statement about the best option for commissioners. It is probable that the procedure will be of benefit to certain carefully defined sub-groups of patients.

Option 1 Await Further Evidence

Do not commission this procedure until further randomised controlled studies, preferably with economic analysis, and with longer periods of follow-up, have demonstrated that the procedure is effective, and there is clear evidence as to which sub-groups of patients are suitable.

Option 2 Commission the Procedure for Selected Sub-groups of Patients

Based on current evidence, this procedure would be commissioned for those sub-groups of patients for whom it appears to be of benefit.

Option 3 Commission the Procedure as Part of Tertiary Cardiology Services

Allow clinicians to use this procedure at their discretion, as one treatment modality within an overall package of tertiary cardiology services.

9. CONCLUSIONS

Across all RCTs there were no significant differences demonstrated in 12 month survival rates. Similarly, peri-operative mortality rates (defined as death within 30 days of the procedure) were generally low, but varied across different studies. Greater rates were generally observed in the case series studies where sample sizes were small. The variation in rates might well reflect differing inclusion criteria or study samples and eliciting an interpretation is not obvious.

If angina relief is defined as a reduction of at least two classes in the CCS score, then the results of all four RCTs imply that there is evidence to suggest that TMLR is effective at relieving the pain of angina. Rates of hospital admissions for angina also suggest that TMLR is effective, but only one study reports the total number of hospital admissions making the clarification of inferences difficult. The use of cardiac medications was also found to be reduced in those patients receiving TMLR.

Two studies (one RCT) demonstrate improvements in myocardial perfusion, but the three remaining RCTs illustrated no improvement. Similarly, LVEF was improved in one of the case series studies, but was not shown to have improved in the two RCTs where it was measured. Exercise capacity was demonstrated to have increased in most studies, though one RCT did not illustrate an increase.

Quality of life was assessed in just four of the studies, using differing instruments, thus making conclusions inconclusive. However, despite such diversity, all four studies reported that improvements in quality of life had been observed in patients who had undergone TMLR.

Based upon these findings, it is unclear whether the benefits of TMLR are clearly proven in these studies. The findings in the four RCTs appear to be contradictory. In addition, it is unclear what the benefits are beyond a 12 month duration following the intervention - the length of follow-up in most of the studies. It is suggested that the clinical evidence does not present conclusive evidence for the superiority of the TMLR procedure and more research is required before unambiguous empirical support can be embraced.

There is insufficient economic analysis at present to reach a firm conclusion about the cost-effectiveness of TMLR. Using available data to model this, however, suggests that the cost per QALY is at least £45,000 and may be considerably more.

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CONFLICTS OF INTEREST

None identified.

EXPIRY DATE

Once the United Kingdom trialists report their results in full then further evidence regarding the suitability of the procedure will become available.

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