Eclipse TMR Holmium Laser System

Information for Use

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Table of Contents

Eclipse TMR Holmium Laser System Information for Use

Caution: Federal law restricts this device to sale by or on the order of a physician (or properly licensed practitioner). Federal law further restricts the use of this device to practitioners who have been trained in laser heart surgery including laser operation.

Caution: Use of this device is restricted to patients who have signed a procedure-specific consent form to ensure that the risks associated with TMR have been fully explained and understood.

1. DEVICE DESCRIPTION

The Eclipse TMR Holmium Laser System (Eclipse TMR System) is composed of the Eclipse TMR 2000 Holmium: YAG laser (TMR 2000), fiberoptic delivery systems and handpieces. The laser radiation emitted from this system has a wavelength of approximately 2.1 microns, which is in the mid-infrared (invisible) range of the electromagnetic spectrum. Water is the target absorber for this laser wavelength. This laser emits 200 microsecond laser radiation pulses at a 5 Hertz pulse repetition rate. The system limits maximum average power to 6-8 Watts (1.2-1.6 Joules/pulse). These pulses are not synchronized with the cardiac cycle, and there is no visible aiming beam.

The laser energy is delivered to the target tissue via fiberoptics. Two fiberoptic systems have been designed for this purpose, a single solid core fiber of approximately 1 mm diameter (CrystalPoint®) and a fiber bundle (CrystalFlex®) composed of 37, 100 micron diameter fibers also with an overall diameter of approximately 1 mm. There are four surgical handpieces which are used to deliver the fiberoptics to the myocardial tissue: SoloGrip® II (with an embedded CrystalFlex® fiber), SoloGrip® I, SoloGrip® IP, and J-Grip® (see Section 11.3 How Supplied).

2. INDICATIONS FOR USAGE

Transmyocardial revascularization with the Eclipse TMR System is indicated for treatment of stable patients with angina (Canadian Cardiovascular Society Class 4) refractory to medical treatment and secondary to objectively demonstrated coronary artery atherosclerosis and with a region of the myocardium with reversible ischemia not amenable to direct coronary revascularization.

3. CONTRAINDICATIONS

No contraindications known.

4. WARNINGS and PRECAUTIONS

- Patients with unstable angina (unweanable from intravenous anti-anginal medications) experienced 11% (16/150) peri-operative mortality (surgery + 30

days) compared to 5% (7/132) in patients who did not require intravenous anti-anginal medications.

- Do not treat the myocardium in the area of a left ventricular mural thrombus because of potential for the creation of emboli.

Explosions or fire hazard - Do not operate the TMR 2000 in the presence of flammable substances, including gases, anesthetics, cleaning agents, combustible materials, or other volatile substances. **Explosions or fire can result.**

- Combustible or flammable materials (for example surgical drapes, gowns or gauze) in the surgical field may be ignited by laser radiation unless they are kept wet or moistened.
- Surround the surgical field with wet towels or wet gauze.
- Modify all other flammable materials to make them fire-retardant (for example flame resistant surgical drapes and gowns). Minimize oxygen exposure as oxygen increases the combustibility of materials exposed to laser radiation.
- The fiberoptic may only be used with an Eclipse TMR laser system.

Laser radiation - The TMR 2000 is classified as a Class IV laser product as defined in the Code of Federal Regulations (CRF 21 Section 1040.10(b)).

- Avoid exposure to laser radiation at all times during the installation and operation of the laser as direct or reflected radiation may damage skin or eyes.
- DO NOT LOOK DIRECTLY INTO THE Ho:YAG LASER BEAM as it can cause permanent ocular damage.
- Protect the patient's eyes by covering them with wet gauze or protective eyewear.
- All operating room personnel must wear protective eyewear with a minimum optical density of 3 at a wavelength of 2.1 μm when the TMR 2000 is in use.

Physician Training

- The Eclipse TMR System should only be used by properly trained surgeons (see Section 12.3 Operator Training).

Handling and Sterilization of CrystalFlex®, CrystalPoint® and SoloGrip® II

- The CrystalFlex® and CrystalPoint® fiberoptics and the SoloGrip® II handpiece are sterilized with EtO gas and are **for single use only**. **Do not re-sterilize or reuse**.
- Inspect sealed sterile package before opening. Product is sterile only in unopened, undamaged package. If package is opened or damaged, or if seal is broken, contents may not be sterile and may cause infection in the patient.
- Do not bend the fiberoptics at sharp angles. If breaks or fractures appear in the fiberoptic, discontinue use and replace with a new fiber.
  - CrystalFlex® fiber should not be bent beyond a bend radius of 1/8 inch.
  - CrystalPoint® fiber should not be bent beyond a bend radius of 1.5 inches.
- **Biohazard** -- After use, handle and dispose of fiberoptic as appropriate for a biohazard.

Handling and Sterilization of SoloGrip® I, SoloGrip® IP and J-Grip®

- The SoloGrip® I, SoloGrip® IP and J-Grip® handpieces are distributed non-sterile in packaging not suitable for sterilization. These products must be steam autoclave sterilized prior to use (See Section 11.2, Clinical Use, if appropriate).

Precautions During TMR

- Avoid fluid loading the patient immediately prior to or during the TMR procedure, since fluid loading was associated with higher mortality in the clinical studies.
- The operator should pause ½ - 2 minutes between the creation of every few TMR channels (2 – 5 channels) since pauses may reduce the likelihood of ventricular arrhythmias following treatment.
- TMR treatment should be limited to the lower 2/3 of the left ventricle to avoid the mitral valve and disruption of the conduction system near the AV groove.
- It is recommended that no more than 50 TMR channels be created, since the safety and effectiveness of more channels has not been studied (10 % of patients in the clinical studies were treated with 51 or more channels).
- The surgeon should have a defibrillator readily available throughout the surgical procedure.
- If the patient experiences ventricular fibrillation during the procedure, discontinue the procedure and treat the arrhythmia as appropriate.
- Patients receiving less reversible anti-coagulant therapy should be changed to heparin prior to the procedure so that anti-coagulation can be more readily reversed.

6. ADVERSE EVENTS

6.1 Observed Adverse Events

The randomized trial of TMR using the Eclipse TMR System versus medical management (MM) involved 275 patients who were followed for a total of 204 patient-years.

There was one intra-operative death in the TMR group, which occurred in a patient who did not receive TMR – the patient developed ventricular fibrillation which could not be converted during preparation of the heart for TMR. Within 30 days of TMR, five other patients died of cardiac causes and one died of pulmonary causes. In the MM group, two patients died within 30 days of enrollment in the study, both due to cardiac causes. During 12 month follow-up, an additional nine patients in the TMR arm died (six due to cardiac causes, one each due to renal causes, multi-system organ failure and sudden death), and an additional five patients died in the MM arm (all due to cardiac causes).

Adverse Events were reviewed by an independent, masked Data Safety and Monitoring Board (DSMB).

Table 1: Adverse Events

All patients in the Randomized Trial (n=275)

Includes all adverse events, both related and unrelated to TMR, sorted alphabetically.

	TMR (N=132)		MM (N=143)	
Adverse Event	**Early (0-30 days)**	**Total (0 days to 1 yr)**	**Early (0-30 days)**	**Total (0 days to 1 yr)**
Any Adverse Event	39% (51)	55% (72)	22% (31)	56% (80)
Angina/Chest Pain Requiring Re-hospitalization	2.3% (3)	17% (22)	16% (23)	44% (63)
Arrhythmia, Atrial	9.8% (13)	11% (14)	0.7% (1)	0.7% (1)
Arrhythmia, Operative Ventricular Fibrillation (Op VF)	8.3% (11)	N/A	N/A	N/A
Arrhythmia, Other ventricular arrhythmia	12% (16)	13% (17)	0% (0)	0% (0)
Congestive Heart Failure	3.8% (5)	5.3% (7)	1.4% (2)	4.2% (6)
Death (all causes)	5.3% (7)	13% [a]	1.6% (2)	8.6% [a]
Dyspnea	0% (0)	0% (0)	1.4% (2)	8.4% (12)
Hypotension	9.8% (13)	11% (14)	0% (0)	0% (0)
Myocardial Infarction				
Q Wave MI	0.8% (1)	1.7% [a]	0.8% (1)	3.8% [a]
Non Q Wave MI	4.5% (6)	12% [a]	0.8% (1)	6.7% [a]
Pleural Effusion	0% (0)	2.3% (3)	0% (0)	0% (0)
Respiratory Insufficiency	3.0% (4)	3.0% (4)	0% (0)	0% (0)
Systemic Infection	1.5% (2)	1.5% (2)	0% (0)	0% (0)
Transfusion Required				
Due to blood loss from TMR	0% (0)	N/A	N/A	N/A
Due to other reasons	1.5% [b] (2)	1.5% (2)	0% (0)	0% (0)
Unstable Requiring I.V. Anti-Anginals	1.5% (2)	17% (22)	19% (27)	48% (68)

The following events were reported only once in patients treated with TMR: allergic reaction, grand mal seizure, hemothorax, cardiomyopathy, pericarditis, peripheral edema, pneumothorax, pulmonary embolus.

The following events were reported only once in patients treated with MM: cardiogenic shock, dehydration, pneumonia.

[a] *Survival estimated using Kaplan-Meier methods*

[b] *1 due to GI bleed, 1 due to pre-existing anemia*

Note: Some patients experienced more than one adverse event

6.2 *Potential Adverse Events*

Adverse events potentially associated with the use of TMR include (in alphabetical order):

- Accidental Laser Hit
- Acute Myocardial Infarction
- Arrhythmia
- Cerebrovascular Accident
- Conduction Pathway Injury
- Congestive Heart Failure
- Death
- Mitral Valve Damage
- Pulmonary Complications
- Unstable Angina

7. CLINICAL STUDIES

Purpose: The purpose of this study was to compare TMR to MM. **Primary outcome measures** were angina improvement, mortality, event-free survival, treatment failure,

changes in perfusion as measured by thallium scans, and frequency of cardiac rehospitalizations.

Design and Patients: This multi-center, prospective, randomized controlled trial was conducted at 18 U.S. centers. In the original study plan, 160 patients were enrolled between March 1996 and February 1997; 74 to TMR and 86 to MM. All 160 patients have reached one year follow-up. Between February 1997 and July 30, 1998, an additional 115 patients (58 TMR, 57 MM) were enrolled in the study. Thus, a total of 275 patients were enrolled in the study through July 30, 1998; 132 were randomized to TMR and 143 were randomized to MM. Baseline characteristics and cardiac risk factors were similar between the two groups. Prior to 12 months, 46 patients in the MM group met *a priori* defined treatment failure criteria, became unstable, were withdrawn from this study, and were enrolled in a separate study of TMR use in unstable patients, leaving 97 patients in the MM group.

Methods: TMR was performed through a left lateral thoracotomy. The handpiece, containing an optical fiber assembly, was applied to the surface of the left ventricle. As the fiber was advanced through the wall, pulsed laser energy was delivered to the myocardium until the optical fiber tip reached the left ventricular cavity. TMR channels were placed approximately 1 cm from each other. The number of channels created ranged from 16 – 87 (mean 39), using a mean energy of 1.4 Joules per pulse (range 1.2 – 1.6 J/pulse) and a mean of 14 pulses/channel.

Results: Table 2 lists the principal safety and effectiveness results. There was statistically significant difference in angina improvement, and 12 month survival (event-free, freedom from treatment failure and freedom from cardiac rehospitalization). There were no apparent differences in perfusion as measured by thallium scans.

Kaplan-Meier survival estimates at 12 months were similar between the 2 groups: 87% for TMR treated patients and 91% for MM patients.

Table 2: Principal Safety and Effectiveness Results

	TMR (n=132)	MM (n=143)	Difference (TMR-MM) [CI]
Angina Improvement at 12 mo.	76% (58/76)	32% (16/50)	44%* [28%, 60%]
Thallium Scan Results at 12 mo. (n=61)			
Mean ± SD Δ Extent Ischemia (%)	-0.9 ± 9.4	-0.6 ± 10.8	-0.3 [-5.0, 5.6]
Mean ± SD Δ Extent Rest Defects (%)	1.6 ± 12.5	2.2 ± 11.8	-0.6 [-5.9, 7.1]
Freedom from All Cause Mortality			
30 Day Survival	95%	98%	3.7% [-1%, 8%]
Survival at 12 mo. (KM)	87%	91%	4.9% [-2.5%, 12.3%]
Event Free Survival at 12 mo. (KM)	55%	31%	24%* [12%, 35%]
Freedom from Treatment Failure at 12 mo. (KM)	74%	48%	26%* [16%, 38%]
Freedom From Hospitalization for Cardiac Causes at 12 mo. (KM)	61%	33%	28%* [17%, 39%]
Medication Use at 12 mo.			
Decrease in Calcium Channel Blockers (% Pts)	56%	24%	32%* [14%, 50%]
Decrease in Beta Blockers (% Pts)	39%	17%	22%* [6%, 39%]
Decrease in Nitrates (% Pts)	39%	24%	15% [-2%, 31%]
Quality of Life (DASI Score) at 12 mo.	21 ± 14	12 ± 11	9* [3.1, 14.9]
Exercise Treadmill Tests at 12 mo.			
Total Exercise Time (min.)	7.9 ± 4.5	6.2 ± 5.6	1.7 [-0.6, 4.0]
Total Workload (METS)	5.0 ± 0.7	3.9 ± 0.8	1.1* [0.0, 2.1]

**=p<0.05 P value calculated using Fisher's exact test, 2-sided for proportions, Student's t-test, two sided for continuous variables, or log rank test for KM survival estimates.*

KM: Kaplan Meier survival estimates

CI=95% confidence interval by normal approximation

Angina Improvement: Improvement in angina symptoms from baseline to 12 months by ≥2 Canadian Cardiovascular Society classes in patients who were available at 12 month follow-up.

Thallium Scans: A negative value indicates an improvement in a parameter. A positive value indicates a worsening.

Event Free Survival: Freedom from death, Q-wave MI, hospitalization for cardiac causes, CABG or percutaneous intervention.

Treatment Failure: Death, Q-wave MI, 2 cardiac hospitalizations within 3 months, 3 cardiac hospitalizations within 1 year, or unweanable from IV anti-anginal medications for at least 48 hours after at least 2 attempts at weaning.

DASI: Duke Activity Status Index for quality of life. A higher score indicates a better quality of life

In the TMR group, five of 23 (22%) patients treated prior to July, 1996 died within 30 days of the procedure. Investigators attributed these deaths to "fluid loading" patients in preparation for the TMR procedure, manipulation of the heart, and not pausing between creation of channels. These practices were altered in June, 1996.

From July, 1996 to completion of enrollment in July, 1998, an additional 109 patients received TMR in the study. In this group 30 day mortality was 1.8% (2/109).

8. PATIENT SELECTION AND TREATMENT

8.1 Specific Patient Populations

The safety and effectiveness of the Eclipse TMR System has not been established for the following specific populations:

- patients under the age of 18;

- patients who are pregnant or undergoing labor and delivery;
- nursing mothers;
- patients suffering from active hepatic disease, renal failure, cancer or major infection;
- patients with a left ventricular ejection fraction less than 25%;
- patients with mechanical heart valves;
- patients with CCS class III or better;
- patients with myocardial ischemia limited to the right ventricular wall.

9. PATIENT COUNSELING INFORMATION

This device is restricted to use in patients who sign an informed consent to ensure that the risks associated with TMR have been fully explained to, and understood by, the patient.

Patients should be advised that any reduction of angina may occur gradually, that they should continue on their antianginal medications, and that the need for these medications will be re-evaluated at subsequent visits.

Patients should be advised of the risks of the procedure including the possibility of:

- recurrence of angina;
- progression of myocardial ischemia;
- worsening heart failure;
- cardiac arrhythmia;
- death.

10. CONFORMANCE TO STANDARDS

The TMR 2000 laser has been tested to and conforms with the requirements of the following domestic and international standards:

- IEC601-1:1988 Medical Electrical Equipment, General Requirements for Safety
- IEC60601-1-2:1993 Medical Electrical Equipment, General Requirements for Safety, Collateral: Electromagnetic
- IEC601-2-22:1992 Medical Electrical Equipment, Particular Requirements for the Safety of Diagnostic and Therapeutic Laser Equipment.
- 21CFR Part 1040.10 Laser Product Performance Standard
- EN55011:1998 Class A, the European Electromagnetic Emissions Standard
- IEC 825-1 Radiation Safety of Laser Products & Equipment

11. HOW SUPPLIED

11.1 Packaging

The Eclipse TMR System consists of the TMR 2000 laser, disposable fiberoptics and handpieces.

- The TMR 2000 laser is initially installed in the hospital by Eclipse personnel.
- The single-use fiberoptics are supplied sterile for every TMR case. Sterility may be compromised if the package is opened or damaged.

11.2 Storage

All fiberoptics and handpieces should be stored under conditions that protect against extremes of temperature and humidity. Products should be stored in a clean, dry environment, protected from water. Do not stack other objects on packaging to avoid crushing. Proper stock rotation should be practiced.

11.3 Fiberoptics and Handpieces

CrystalPoint®	Single-fiberoptic to deliver laser energy
CrystalFlex®	Multiple-fiberoptic bundle to deliver laser energy
SoloGrip® II	Single-handed disposable handpiece with integrated CrystalFlex® fiberoptic
SoloGrip® I	Single-handed reusable handpiece to deliver CrystalFlex® fiberoptic
SoloGrip® IP	Single-handed reusable handpiece with Grip-tip® to deliver CrystalFlex® fiberoptic
J-Grip®	Reusable handpiece to deliver CrystalFlex® fiberoptic

12. CLINICIAN USE INFORMATION

12.1 Patient Informed Consent

In addition to the standard surgical consent, Eclipse Surgical Technologies requires a standard consent form to be signed by each patient to ensure that the risks associated with TMR have been fully explained to the patient.

12.2 Device Operating Instructions

Operating instructions for the laser unit are contained in the TMR 2000 Laser User Manual which includes sections describing the system specifications, operation of the laser, laser safety, labeling, and troubleshooting. It also contains a glossary of laser terms.

It is essential that the User Manual, especially those parts dealing with laser safety, be read and understood before operating, maintaining, or servicing this system. Failure to operate the TMR 2000 laser in accordance with the User Manual may result in serious injury.

Specific instructions for use are provided with each fiberoptic delivery system and should be read in conjunction with this Information For Use document.

12.3 Operator Training

Federal law restricts the use of this device to practitioners who have been trained in laser heart surgery including laser system operation. Operator training for use of the Eclipse TMR System must include training in the use of the laser system, fiberoptics and handpieces, as well as appropriate clinical training.

Laser Training:

The American National Standards Institute offers the following Standard of Practice for the Use of Lasers in Medicine and Surgery:

ANSI Z136.3, "American National Standard for Safe Use of Lasers in Health Care Facilities," 1996.

Clinical Training:

Use of the Eclipse TMR System should only be undertaken by personnel who have met the standards of the Eclipse continuing education training program, which includes didactic and hands-on training covering:

- patient selection
- surgical technique
- patient management

Further information about training can be obtained from an Eclipse Surgical Technologies, Inc. representative at 800-238-2205.

12.4 Mechanism of Action

The mechanism(s) whereby TMR relieves angina is not known. In addition to possible contributions of placebo effect, current theories include:

- Increased perfusion of myocardium via the channels created;
- Increased collateralization via angiogenesis;
- Symptom reduction resulting from disruption of pain fiber function;
- Possible microinfarcts to the myocardium.

13. PATIENT'S MANUAL

The brochure "Questions & Answers about Transmyocardial Revascularization (TMR)" provides general information to the potential patient regarding the risks and benefits associated with the TMR treatment.

---------- end of device labeling ----------

TMR may not be appropriate for you if:

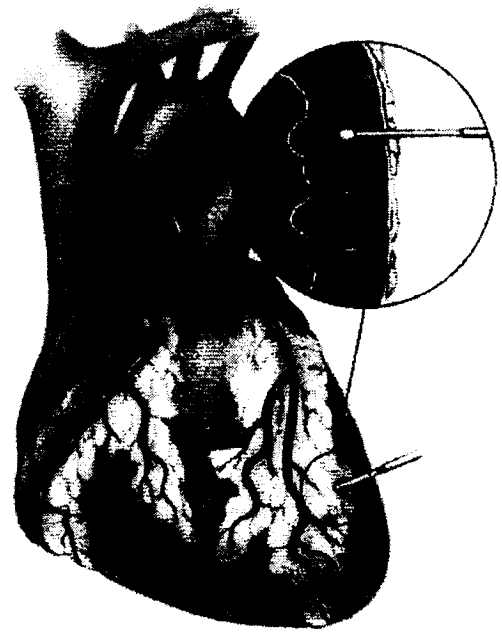
- you are unable to undergo general anesthesia.
- you have had a heart attack (myocardial infarction) within three weeks.
- you have uncontrollable or severe heart rhythm problems.
- you have debilitating chronic lung disease such as chronic obstructive pulmonary disease which significantly impairs your ability to breathe.
- you have heart failure, also known as congestive heart failure, usually associated with shortness of breath due to "fluid in the lungs" or with swelling in the lower extremities.

TMR May Benefit You if there is an area of your heart which is not receiving enough oxygen and cannot be treated by balloon angioplasty or bypass surgery.

- Treatment with TMR may reduce your angina pain and help you return to a more active lifestyle.
- Treatment with TMR may also reduce your need for some of the medications you are currently taking to manage your angina pain.
- TMR has been shown to reduce angina and improve the quality of life in patients with coronary artery disease.
- It is important that you understand the risks and benefits of this new procedure, and that you discuss them with your doctor. If your doctor recommends that you have the TMR surgery, then you will be asked to sign an additional informed consent explaining these risks and benefits.

Information for Patients Considering

Transmyocardial Revascularization (TMR)



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What is angina and why do I have it?

All cells, muscles, and tissues in your body need the oxygen carried in your blood. This is the same for your body's main blood pump, the heart muscle. If blood vessels which bring blood to the heart muscle are clogged or damaged, the heart muscle doesn't get the oxygen it needs and you feel a pain in your chest, neck, jaw or shoulders, called angina. This pain can limit your physical activity and ability to do the things you want to do.

It is important that you understand the risks and benefits of this new procedure, and that you discuss them with your doctor. If your doctor recommends that you have the TMR surgery, then you will be asked to sign an additional informed consent explaining these risks and benefits.

What is TMR?

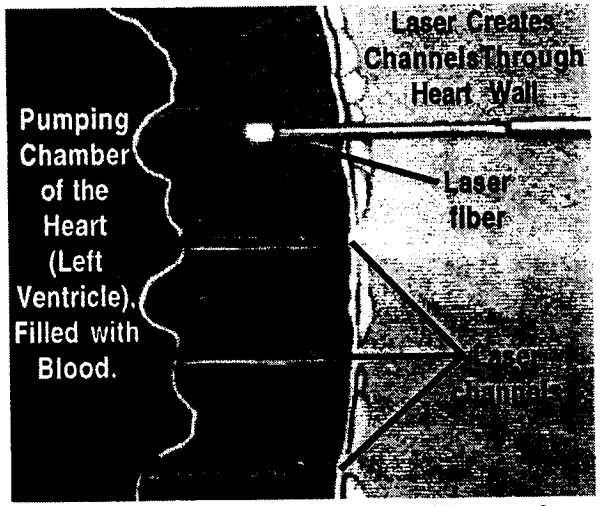
Transmyocardial **R**evascularization, or **TMR**, is a new surgical procedure which uses a laser to make 20 - 45 "channels," or small holes, directly into the heart muscle. The outside of the heart muscle seals up immediately. TMR has been shown to reduce angina and improve the quality of life in patients with coronary artery disease. This laser for TMR was approved by the U.S. FDA as a safe and effective device for the treatment of angina due to advanced cardiovascular disease.

At this time, it is not fully understood how TMR relieves angina. In addition to possible contributions of placebo effect, current theories that are under investigation for the way in which TMR works include:

- by directly increasing the blood flow to the heart muscle,
- by stimulating the growth of new small blood vessels within the heart muscle, and/or
- by reducing the sensation of pain you feel from angina.

How many and how big are the channels created by TMR?

Your surgeon will decide how many channels should be placed into your heart muscle and where they should be placed. Generally, though, no more than 45 channels are made. The channels are one-half inch apart and are a little bigger around than a standard sewing needle.



Cross-section of the heart with TMR procedure

Is there much bleeding or blood loss associated with the procedure?

It is unusual for there to be any significant bleeding as a result of these channels. The bleeding that occurs is normally stopped with mild manual pressure at the channel site and rarely has any TMR patient required a blood transfusion as a result of the channels.

Am I a candidate for TMR?

You may be a candidate for the TMR procedure if:

- you have angina due to advanced cardiovascular disease.
- you are not a candidate for standard therapy (for example balloon angioplasty or bypass surgery).
- the heart muscle around these affected blood vessels is healthy.
- your angina cannot be managed with medications or these medications are causing serious side effects.

What are the risks associated with TMR?

TMR requires a surgical procedure and there are risks associated with the surgery in general and with the TMR procedure itself, including:

- risks normally associated with chest surgery, such as death, heart attack (myocardial infarction), stroke, and heart failure,
- risk of disruption of normal rhythm of the heart during and/or after the procedure.

Your doctor will discuss all the risks and benefits of surgery and the TMR procedure with you.

What follow-up will I receive?

Your follow-up requirements for recovery after a TMR procedure are similar to those following other heart surgeries. You will undergo regular check-ups by your physician. Your physician will advise you when you may return to more normal activities.