Transmyocardial Laser Revascularization: A Consensus Statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2006

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INTRODUCTION

Dramatic advances in coronary revascularization techniques have been developed in recent years. Improved technologies and techniques for coronary artery surgery and percutaneous coronary intervention have allowed for treatment of coronary vessels that were previously considered inaccessible or not amenable to conventional treatment.[1] In addition, pharmacologic management of chronic angina has improved clinical outcomes.[2]

Despite advances in pharmacologic therapies and catheter-based or surgical revascularization techniques, a significant number of patients with angina are poor candidates for traditional methods of treatment because of diffuse coronary disease, small distal vessels, or other comorbidities.[3] Additional options are required for patients with angina refractory to maximal medical therapy who are not candidates for catheter-based therapy or bypass surgery or in whom these methods have failed.[4]

Whether transmyocardial laser revascularization (TMR) represents a potential option for these patients has been explored in a number of clinical trials. Given that the evidence base has begun to grow in this area and considering that decisions will need to be made regarding uptake of this procedure into practice, there is a need for international consensus regarding the evidence for the balance of benefit and risks of TMR relative to continued maximal medical therapy (MMT).

METHODS

Purpose of the Consensus Conference

This consensus conference was held to clarify, for clinical practitioners and health care planners or administrators, the role of transmyocardial laser revascularization relative to conventional methods of revascularization in adults experiencing refractory angina. Although interest in TMR has increased in some centers and has decreased in others, the inconsistent response to its uptake highlights the need for exhaustive review of the evidence for and against TMR. Given the controversial nature of TMR, an objective and unbiased review of best available evidence from randomized trials will be key in defining what its potential role should be in contemporary practice. A secondary objective of this consensus conference was to identify the gaps in the evidence and suggest a future research agenda for TMR.

Funding

Support for this consensus conference was provided by the International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS), which has received unrestricted educational grants from industries that produce surgical technologies. However, this consensus conference did not involve direct or indirect funding from manufacturers of technologies related to TMR. Editorial independence was granted to the members of the expert panel, and the expectation was that the resulting consensus statements would be clearly based on the best available evidence, with explicit methodology to allow the user to determine which aspects were informed by evidence and which aspects were not adequately informed by evidence and where opinion was required to create statements.

Selection of Panel Members

Members of the consensus panel were invited to participate by the chair and facilitator of the consensus process. Members included representation from five countries: six cardiovascular surgeons, one cardiologist, one cardiac anes-

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thesiologist (Canada), and one methodologist with expertise in health technology assessment and meta-analysis (Canada).

Defining the Clinical Questions

Before the consensus conference, the consensus panel was required to define the clinical questions, including the scope and depth of each of the following considerations: patient population of interest, intervention of interest, valid comparator group(s), and outcomes of interest. Two clinical questions decided on by panel were stated as follows:

I. Does TMR improve clinical and resource outcomes compared with MMT in chronic angina patients with coronary artery and myocardial morphology deemed not amenable to revascularization?
II. Does TMR adjunctive to CABG (TMR + CABG) improve clinical and resource outcomes compared with CABG alone in patients with chronic angina with coronary morphology deemed only partially amenable to revascularization by conventional revascularization?

Specific clinical and resource outcomes of interest were defined across the following three categories

1. Symptoms and quality of life (QOL)
   a. Angina severity, angina class improvement, need for medications
   b. Seattle Angina Questionnaire (SAQ), Euro-QOL, SF-36, SF-12, patient satisfaction
2. Perioperative and long-term complications
   a. Death, myocardial infarction, stroke or transient ischemic attack, renal failure, bleeding, transfusion, major adverse coronary events (MACE), heart failure, need for reintervention
   b. Imaging studies: perfusion, wall motion, ejection fraction
3. Resource utilization
   a. Procedure time, ICU and hospital length of stay, readmission
   b. Costs and cost-effectiveness

Identifying Relevant Evidence

After the clinical questions had been defined, the admissible evidence (ie, acceptable study designs) to inform this clinical question was defined by the consensus panel as any randomized or nonrandomized comparative trial, whether published or unpublished in any language, comparing:

a) TMR versus MMT in adults with refractory angina not amenable to conventional CABG, or
b) TMR + CABG versus CABG alone in adults undergoing CABG who had coronary artery morphology only partially amenable to conventional revascularization.

Since there was no current comprehensive systematic review that included all relevant evidence to address these clinical questions, we conducted a full systematic review and meta-analysis of the evidence prior to the conference. The complete methodology and results of the systematic review

has been described in a companion paper in this issue of the *Journal*.[5] In short, comprehensive searches of Cochrane, Medline, Embase, and other databases were conducted to identify all randomized and nonrandomized comparative trials of TMR versus MMT or TMR + CABG versus CABG that reported clinical- or resource-related outcomes from the earliest available date to March 2006. Potentially relevant trials were circulated to the consensus panel for review and to determine whether any relevant trials were missed. Information related to baseline characteristics and outcomes was extracted and confirmed by two authors from each study who met prospectively defined inclusion criteria. When appropriate, data were synthesized by meta-analysis to determine aggregate estimates of clinical and resource-related outcomes. Data that were not appropriate for statistical synthesis across trials were summarized qualitatively in tables and text to ensure all relevant evidence was addressed in the systematic review. The results of the systematic review and meta-analysis were used to populate evidence tables to form the basis for discussions and support the decision-making of the consensus panel. Complete evidence to inform the benefits, risks, and resource considerations of TMR was sought.

Reviewing and Presenting the Evidence

Before the consensus conference, each member of the consensus panel received a copy of all identified randomized and nonrandomized clinical trials and relevant background literature related to the clinical question. In advance of the meeting, members of the consensus panel reviewed the evidence for TMR versus conventional treatments relevant to each of the following subquestions:

1. Does TMR improve symptoms and QOL versus MMT?
2. Does TMR improve perioperative and long-term complications versus MMT?
3. Does TMR improve resource utilization versus MMT?
4. Does TMR + CABG improve symptoms and QOL versus CABG?
5. Does TMR + CABG improve perioperative and long-term complications versus CABG?
6. Does TMR + CABG improve resource utilization versus CABG?

Applying the Evidence to Create Recommendations

Levels of Evidence and Grade of Recommendations

The best available evidence that was used to inform each clinical subquestion was classified according to the taxonomy suggested by the American Heart Association/American College of Cardiology (AHA/ACC), as outlined in Table 1. This classification categorizes the evidence based on study design and susceptibility to bias, wherein higher levels of evidence and grades are labeled to highlight their lesser likelihood for bias and increased confidence in "closeness to the truth."[6–8] Several systems of grading recommendations and labeling the strength of evidence exist. Since none of them have been found to be superior, the AHA/ACC system was chosen for consistency with other guidelines [http://

TABLE 1. Levels of Evidence

Level of evidence A
Data derived from multiple randomized clinical trials
Level of evidence B
Data derived from a single randomized trial, or nonrandomized studies
Level of evidence C
Consensus opinion of experts

www.acc.org/clinical/manual/manual_index.htm accessed April 19, 2004] (See Tables 1 and 2). As recommended by guidelines,[9] classification of the evidence and labeling recommendations is best done by the group panel, using a democratic voting process after group discussion of the strength of the evidence.

Members of the panel considered the highest possible level of evidence to inform their clinical subquestion, such that systematic reviews or meta-analyses or randomized trials [level A evidence, See Table 1] were to be considered preferentially to nonrandomized clinical trials. If there was insufficient level A evidence to inform the question, members were encouraged to consult nonrandomized comparative trials [level B evidence, See Table 1]. Whereas level C evidence (ie, noncomparative studies, such as case series) was collected and distributed to the panel members for review, level C evidence was not used for creating the evidence-based statements. When evidence from published or unpublished clinical trials to address the question was nonexistent, expert opinion from the consensus panel members informed by level C evidence was consulted. In each case, the best available level of evidence was explicitly stated, and interpreted in light of its methodologic strengths and weaknesses before a statement of recommendation was made. It was agreed that recommendations with higher levels of evidence should be interpreted with more confidence than recommendations based on lower levels of evidence, and that recommendations should be explicitly classified as per the ACC/AHA system [See Table 2].

Consensus Process and the Role of Evidence Versus Opinion

At the consensus meeting, the meta-analysis of all level A and level B evidence was presented to the entire consensus panel. After presentation of the evidence, further discussion of the strength, consistency, clinical significance, and relevance of the evidence occurred before draft evidence-based statements and recommendations were proposed by the group. Final revisions and agreement was made through further discus-

sion. Legitimate conflicts over values and interpretations were resolved by open discussion and majority vote.

After each subquestion had been addressed, the entire consensus panel reviewed all of the recommendations and their assigned grades of recommendations and proposed levels of evidence to answer the overarching summary clinical questions: What is the role of TMR compared with MMT in adults with refractory angina not amenable to conventional surgical revascularization? What is the role of TMR + CABG compared with CABG alone in chronic angina patients with coronary morphology deemed only partially amenable to revascularization by conventional revascularization?

In summary, the purpose of this consensus process was to provide comprehensive evidence-based statements while allowing for opinions to inform recommendations only when information was incomplete and requiring that the basis for the statement be labeled by a declarative level of evidence. Bringing experts (protagonists and antagonists) together in a consensus process allowed for breadth of perspectives and representations of interpretations for a carefully considered judgment of the evidence.

RESULTS

Consideration of all studies within the systematic review and meta-analysis formed the basis for the discussion and directed the formation of recommendations.[5]

A total of nine randomized trials (six TMR versus MMT[10–15]; three TMR + CABG versus CABG[16–19]) and three nonrandomized trials (TMR + CABG versus CABG[20–22]) published in 23 papers were considered in the meta-analysis.[5] All included studies were published in English. No unpublished studies were identified.

The aggregate results for randomized, controlled trials (RCTs, level A) from the meta-analysis are preferentially reported here; however, when randomized trials were unavailable, aggregate results from nonrandomized evidence (nRCTs, level B) will be reported. Readers may consult the original publication for comprehensive reporting of both randomized and nonrandomized trials for all end points.[5] For discrete outcomes, odds ratios and their 95% confidence intervals (OR, 95% CI) are reported. For continuous outcomes, the weighted mean difference (WMD, 95% CI) or standardized mean difference (SMD, 95% CI) is reported.

Part A: TMR Versus MMT

Question 1: Does TMR Improve Symptoms and Quality of Life Versus MMT?

Outcomes of interest included angina class improvement, angina severity, exercise performance, and QOL.

TABLE 2. Classes of Recommendations

Class I:	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective
Class II:	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
IIa.	Weight of evidence/opinion is in favor of usefulness /efficacy
IIb.	Usefulness/efficacy is less well established by evidence/opinion
Class III:	Conditions for which there is evidence and/or general agreement that the procedure/treatment is NOT useful/effective, and in some cases may be harmful

For the end point of angina severity, the most commonly reported outcome was an improvement in angina class by ≥2 classes (either CCS or NYHA class). A total of six studies reported this outcome at 1 year (six RCTs, no nRCTs). Overall, the likelihood of achieving ≥2 angina class improvement at 1 year was increased by nearly 8 times [OR, 7.91; 95% CI, 3.33 to 18.80, $P < 0.0001$; six RCTs, level A], and at 3 to 5 years' follow-up was increased by nearly 9 times [OR, 9.20; 95% CI, 3.52 to 24.07, $P < 0.0001$; two RCTs, level A]. Similar results were found at 3 months' and 6 months' follow-up. The estimated number needed to treat with TMR to result in an additional patient achieving ≥2 class improvement compared with MMT was 2 to 3 at each time point (3 months, 6 months, 1 year, and up to 5 years). Subanalyses by type of laser modality suggested that, regardless of which laser was used, the likelihood of achieving ≥2 angina class improvement was increased severalfold. Adequate subgroup comparisons were not possible between laser modalities due to the small number of studies available for subgroup analysis (ie, three RCTs evaluated CO_2 laser; two RCTs evaluated Ho: YAG laser; one study evaluated XeCl laser). Similarly, subanalyses by class of angina at study entry suggested that patients achieved significant improvement regardless of whether they were class III or class IV angina at study entry.

Patients with remaining severe angina (class III or IV) at 1 year was significantly reduced by 94% [OR, 0.06; 95% CI, 0.01 to 0.27], $P < 0.0001$; three RCTs, level A]. Patients with continued angina at 5 years was also significantly reduced [OR, 0.25; 95% CI, 0.08 to 0.83, $P = 0.02$; one RCT, level B].

Quality of life scores at 1 year were reported in three randomized trials. Overall QOL scores were reported in two studies and were significantly improved with TMR versus MMT [SMD, 0.74; 95% CI, 0.49 to 1.00, $P < 0.001$, level A]. SAQ physical limitation scores were reported in two studies and were significantly improved at 1 year [WMD, 19.39; 95% CI, 3.40 to 25.30, $P = 0.02$; level A]. Improvements in other domains of the SAQ score did not reach statistical significance (two RCTs, level A). One study each reported SF-36 scores at 1 year and EuroQOL scores at 1 year. The physical component score of the SF-36 was significantly improved (one RCT, level B) and two of five domains of the EuroQOL were significantly improved (one RCT, level B). Improvements in the remaining domains did not reach statistical significance.

Statement

1) TMR reduces angina by ≥2 classes at 1 to 5 years compared with MMT [level A].
2) TMR improves freedom from class III or IV angina at 1 to 5 years compared with MMT [level A].
3) TMR improves some QOL scores compared with MMT at 1 year [level A].

Recommendation

In stable patients with severe angina not amenable to conventional revascularization, TMR can be recommended to provide sustained angina relief compared with MMT alone (class I, level A evidence).

Question 2: Does TMR Improve Perioperative and Long-term Complications Versus MMT?

Outcomes of interest for this question included death, myocardial infarction, stroke or transient ischemic attack, MACE, heart failure, and reintervention. In addition, stress test results and imaging studies (perfusion, wall motion, ejection fraction) were of interest.

All-cause mortality was not significantly different between groups at 1 year [OR, 1.08; 95% CI, 0.60 to 1.95, $P = 0.79$, seven RCTs, level A] and at 3 to 5 years follow-up [OR, 0.65; 95% CI, 0.41 to 1.05, $P = 0.08$; two RCTs, level A]. Importantly, there was a trend toward reduction in mortality at 3 to 5 years for TMR that did not reach statistical significance ($P = 0.08$). Important differences in subgroup analyses by laser type or by angina severity at study entry were not found; however, subgroup analysis was inadequately powered.

While all-cause mortality was not significantly different between groups at 30 days [OR, 2.08; 95% CI, 0.85 to 5.09, $P = 0.11$, five RCTs, level A], there was a trend toward increased early mortality with TMR versus MMT. Given this data, the possibility that there may exist a true increase in early mortality cannot be ruled out at this time. But, if the difference does exist, it is not large (3.8% mortality for TMR versus 1.8% mortality for MMT). Further studies are required to delineate more accurately the short-term and long-term mortality.

Major adverse coronary events was significantly reduced with TMR compared with MMT at 1 year [OR, 0.23; 95% CI, 0.15 to 0.34, $P < 0.0001$; two RCTs, level A]. No significant difference was found for stroke and myocardial infarction. Heart failure (variously defined, but typically including increases in ACE inhibitor or diuretic use) was significantly increased at 1 to 5 years [OR, 2.65; 95% CI, 1.45 to 4.85, $P = 0.002$; three RCTs, level A]; however, left ventricular ejection fraction was not significantly different between TMR and MMT at 1 year [WMD, –2.44; 95% CI, –5.28 to 0.40, $P = 0.09$; three RCTs, level A].

Change in exercise tolerance testing (ETT) time at 12 months was significantly improved for TMR versus MMT [WMD, 69.00 seconds; 95% CI, 27.14 to 110.86 seconds, $P = 0.001$; one RCT, level B]. Patients experiencing angina that limited exercise time on ETT was significantly improved at 1 year [OR, 0.35; 95% CI, 0.23 to 0.54, $P < 0.0001$; three RCTs, level A].

There was no convincing evidence of improved perfusion with TMR versus MMT (four RCTs showed no difference, one trial suggested improved perfusion on a small subset of data; however, this latter trial was confounded by large loss to follow-up).

Statements

1. In stable patients with class III or IV angina and EF >25% to 30%, TMR has a 30-day mortality

risk compared with 1.8% for MMT (*P* = 0.11). Survival at 5 years shows a trend favoring TMR (*P* = 0.08) [level A].

2. TMR reduces MACE at 1 to 5 years compared with MMT [level A].
3. At 1 year, TMR does not improve ventricular function, may increase ACEI or diuretic usage, and prolongs ETT compared with MMT [level A].
4. TMR does not consistently improve myocardial perfusion [level A].

Recommendation

TMR can be recommended to reduce MACE and prolong ETT in stable patients with refractory severe angina who are not candidates for conventional revascularization [class I, level A evidence].

Question 3: Does TMR Improve Resource Utilization Versus MMT?

Outcomes of interest included ICU and hospital length of stay, readmissions, need for reintervention, and overall costs or cost-effectiveness.

Reductions in readmissions to hospital within 1 year did were significantly reduced for TMR versus MMT [OR, 0.27; 95% CI, 0.17 to 0.40; *P* < 0.0001, three RCTs, level A]. Need for reintervention for ischemia was significantly reduced for TMR versus MMT at 5 years [OR, 0.43; 95% CI, 0.25 to 0.72, *P* = 0.002, one RCT, level B]. Hospital and ICU length of stay data was not provided in the randomized trials. Comparative incremental cost effectiveness was estimated in only one trial.

Statement

TMR reduces hospital readmissions and cardiac reinterventions compared with MMT at 1 year [level A].

Impact of TMR on costs compared with MMT remains undefined [level C].

Recommendation

TMR can be recommended to reduce readmissions and reinterventions in stable patients with refractory severe angina who are not candidates for conventional revascularization [class I].

Part B: TMR + CABG Versus CABG Alone

Question 1: Does TMR + CABG Improve Symptoms/QOL Versus CABG?

Outcomes of interest included angina class improvement, angina severity, exercise performance, and QOL scores.

Angina class was not significantly improved at 12 months [WMD, 0.01; 95% CI, −0.20 to 0.23, *P* = 0.91; two RCTs, level A]. At 5 years, angina class was significantly improved with TMR + CABG versus CABG alone; however, the absolute difference was small [WMD, −0.21; 95% CI, −0.39 to −0.03, *P* = 0.02, three RCTs, level A]. Patients with remaining severe angina at 1 year and up to 5 years was not significantly different between groups. The proportion

ofpatients achieving ≥2 angina class improvement was not reported in the studies.

Quality-of-life scores were reported in only one nonrandomized trial. Although most scores were improved with TMR + CABG at 1 year, none of the domains reached statistical significance.

Statement

At 1 year, adjunctive TMR does not reduce angina class or incidence of angina class III or IV compared with CABG alone [level A].

At 5 years, adjunctive TMR reduces angina class, but the clinical significance remains uncertain [level A].

Adjunctive TMR does not improve exercise performance compared with CABG alone at 1 year [level B].

Impact of adjunctive TMR compared with CABG on QOL remains undefined [level C].

Recommendation

Adjunctive TMR can be recommended to improve long term angina relief in patients with diffuse CAD who cannot be completely revascularized by CABG alone [class IIa].

Question 2: Does TMR + CABG Improve Perioperative and Long-term Complications Versus CABG?

Outcomes of interest for this question included death, myocardial infarction, stroke or transient ischemic attack, MACE, acute myocardial infarction, stroke, cardiac arrest, tamponade, heart failure, and renal failure. In addition, stress test results and imaging studies (perfusion, wall motion, ejection fraction) were of interest.

Survival at 30 days was significantly improved with TMR + CABG versus CABG alone [OR, 0.27; 95% CI, 0.095 to 0.77, *P* = 0.014; three RCTs, level A]. Survival at 1 year [OR, 0.58; 95% CI, 0.38 to 1.18, *P* = 0.13, 3 RCTs, level A] and 4 to 5 years [OR, 0.91; 95% CI, 0.48 to 1.72, *P* = 0.78, two RCTs, level A] did not reach statistical significance. MACE was significantly reduced at 30 days [OR, 0.31; 95% CI, 0.10 to 0.99, *P* = 0.048, one RCT, level B] but not at 1 year [OR, 0.70; 95% CI, 0.36 to 1.37, *P* = 0.30, two RCTs, level A] or 4 years [OR, 0.36; 95% CI, 0.06 to 1.14, *P* = 0.074, one RCT, level A]. Other morbidities, including acute myocardial infarction, stroke, cardiac arrest, tamponade, heart failure, and renal failure were not statistically significantly different between groups.

Change in ETT at 12 to 18 months was significantly improved with TMR + CABG [WMD, 88.05 seconds; 95% CI, 52.8 to 123 seconds, *P* < 0.0001, two RCTs, level A] but no longer at 5 years [WMD, 10.9 seconds; 95% CI, −28 to 50 seconds, *P* = 0.58, one RCT, level A].

Statement

Adjunctive TMR reduces mortality rates and MACE at 30 days but not at 5 years [level A].

Adjunctive TMR does not increase perioperative complications compared with CABG alone [level A/B].

Recommendation

Adjunctive TMR can be recommended to reduce 30-day mortality and MACE in patients with diffuse CAD who cannot be completely revascularized by CABG alone [class IIa].

Question 3: Does TMR + CABG Improve Resource Utilization Versus CABG?

Outcomes of interest included ICU and hospital length of stay, readmissions, need for reintervention, excessive bleeding, cardiopulmonary bypass time, ventilation time, and overall costs or cost-effectiveness.

Cardiopulmonary bypass time [level A], ventilation time [level B], and ICU length of stay [level A] did not differ between groups. However, total hospital length of stay was significantly increased with TMR + CABG versus CABG [WMD, 1.55 days; 95% CI, 0.96 to 2.13 days, $P < 0.0001$, one RCT, level B]. Reoperation [level A], excess bleeding [level B], and readmissions [level A] did not significantly differ. Need for reintervention at 1 year did not reach statistical significance at 1 year [OR, 0.18; 95% CI, 0.03 to 1.08, $P = 0.06$, two RCTs, level A] and 4 to 5 years [OR, 0.38; 95% CI, 0.02 to 6.66, $P = 0.5$, two RCTs, level A].

Statement

1. Adjunctive TMR does not prolong ICU and hospital length of stay compared with CABG alone in patients with diffuse CAD who cannot be conventionally revascularized [level A/B].
2. Adjunctive TMR does not reduce readmissions and reinterventions at 1 to 5 years [level A/B].

Recommendation

None.

Consensus Summary for Overarching Question

After reviewing each of the substatements for the three subquestions for the key clinical questions (TMR versus MMT and TMR + CABG versus CABG), the consensus panel discussed what should be the overall role of TMR to address the overarching question. Since there are no studies that examine a policy of TMR as standard of care, the maximal level of evidence for this recommendation is level B.

Recommendation

TMR represents a viable alternative to conventional maximal medical treatment for patients with refractory stable angina not amenable to conventional surgical revascularization [class I, level B].

Adjunctive TMR + CABG can be considered a part of the therapeutic armamentarium in chronic stable angina patients with coronary morphology deemed only partially amenable to revascularization by conventional surgical revascularization [class IIa, level B].

Statement on Future Research

A number of gaps in the evidence were identified throughout the consensus process. Based on discussion of the limitations of the evidence base, the following areas were suggested by the consensus panel as priority areas for future research:

- Future trials should evaluate the mechanisms responsible for symptomatic improvement after TMR to augment the effect and combine this approach with biological interventions.
- The combination of TMR with novel biological treatments that amplify angiogenesis and myocardial cellular repair may extend the indications of TMR to patients with poor ventricular function.
- Future trials should seek to provide understanding of the mechanisms of early survival benefit after adjunctive TMR to augment this effect and to determine potential synergisms with other myocardial protective strategies.

DISCUSSION

This consensus conference was based on a systematic approach to defining the relevant questions to be addressed, identifying and synthesizing all published and unpublished evidence, and labeling the evidence explicitly to allow decision makers to understand the basis for the recommendations. These statements provided represent the best available guideline for evidence-based clinical practice and resource-related decisions. These statements should be interpreted and applied with full acknowledgment of the underlying level of evidence. In particular, statements based on level A evidence should be applied with more confidence than those of level B or less.[23]

Overall, the evidence based statements reveal that TMR has advantages compared with MMT with respect to angina symptom relief, improved exercise performance and quality of life, reduced major coronary adverse events, and reduced readmissions and reinterventions. For other end points, no significant difference was found for either technique. For only one of the reported clinical end points (heart failure, typically defined as necessity for ACE inhibitors or diuretics) TMR was found to be less favorable than MMT. For other end points, no significant difference was found for either technique. However, two important trends should be discussed. Although these trends should not be overstated given that their confidence intervals incorporate the point of equivalence, it is worthy to note that 30-day mortality showed a potential trend toward a small absolute increase (about 1%) with TMR versus MMT. Whether this is a real effect requires more study, but should be maintained as a possible caveat when considering TMR. Nevertheless, the longer term survival shows a trend favorable toward TMR. Thus, there may be a time trend with TMR, whereby an early risk is undertaken for an overall longer term benefit in favor of TMR.

Although there were three randomized trials that provided follow-up of longer-term clinical outcomes (3 to 5 years), there was loss to follow-up within the trials, which jeopardizes accurate estimates of clinical outcomes.[5] The differing loss to follow-up across the trials may account for some of the heterogeneity that was observed across the trials for longer-term outcomes. Whereas one trial demonstrated a definitive increased likelihood of survival with TMR versus MMT,[11] another trial showed no significant difference.[10] The

difference in longer-term mortality shown between studies may be related to differing demographics (65% versus 100% class IV angina at baseline for Aaberge and Allen, respectively), or differing losses to follow-up over time.

For TMR + CABG, the addition of TMR to CABG does not reduce angina symptoms or exercise performance at 1 year. Although TMR may reduce symptoms at 5 years, the absolute impact was small, and the clinical relevance unknown. Survival and MACE at 30 days were improved, but not at 5 years. Overall impact of adjunctive TMR compared with CABG on QOL remains undefined. Furthermore, the overall impact on length of stay, readmissions, and reinterventions remains equivocal. The paucity of trials for TMR + CABG versus CABG precludes definitive conclusions about most clinically relevant outcomes.

Strengths and Limitations

This consensus statement is based on a current and comprehensive systematic review of the evidence, with formal consensus processes that limited the role of opinion secondary to that of the evidence base. Care was taken to explicitly label the recommendations with the evidence available to inform it, and, when evidence was unavailable, to apply considered expert judgment to provide perspective for potential users of the statement. With this explicit evidence based consensus process, it is clear to the user how the recommendations were derived. The statements have also been exposed to the rigors of secondary panel review, and subsequent external peer review before publication. The methodology undertaken and recommendations provided by this consensus conference are in agreement with current recommendations for developing consensus statements[9] and guidelines[24].

This consensus statement should also be interpreted in light of its underlying weaknesses. Although a wide range of health care professionals and methodologic expertise was represented on the consensus panel, key stakeholders were not represented including patients or laypersons and stakeholders from the manufacturing sector. Clinicians may overestimate the effectiveness of new interventions, especially if the intervention in question rests within the realm of their expertise[25]. In addition, there is a tendency for group decision-making processes to experience "regression to the mean" or groupthink, whereby compromises are made in recommendations to come closest to pleasing all members of the panel, even for greatly polarized issues. To mitigate these risks, clinicians and experts in evidence-based methodology and health technology assessment from within and outside of the surgical field were invited to facilitate the discussion and to ensure the best available evidence was the focus for discussion rather than opinions or political charges. Unfortunately, there were insufficient numbers of studies to test whether publication bias may have affected the results. Publication bias refers to the risk of negative studies remaining unpublished more frequently than positive studies. Given that publication bias cannot be ruled out, which could reduce the magnitude of effect size estimates given here, the results should be interpreted with this caveat in mind. However, it is encouraging that for many of the statistically significant outcomes reported by existing published studies, there was little concerning heterogeneity among the results across the studies. It is also unlikely that many unpublished studies were missed by the authors of this consensus statement, given that unpublished studies were sought by soliciting experts within the field.

Other limitations related to the evidence included those related to shortcomings within the trials, such as nonblinded assessment of angina class in some studies, nonintention to treat analysis of patients who crossed over from the control group to the treatment group (or vice versa), inadequate power for detection of small increases in perioperative complications including death, and variation in the definitions of angina relief, QOL, and ETT. A further limitation relates to the exclusion of patients with unstable angina from most studies included in the systematic review. Studies of TMR for patients with unstable angina will be needed before explicit recommendations can be made for its role in this patient population. Heterogeneity among the trials' inclusion criteria (ie, only one trial required proof of protected myocardium) and variation in outcomes definitions and time horizons of the

TABLE 3. Summary Consensus Recommendations

Class of Recommendation and Level of Evidence	ISMICS Consensus Recommendations
Class I, level A	In stable patients with refractory severe angina not amenable to conventional revascularization, TMR can be recommended instead of MMT alone:
	To improve sustained angina relief [class I, level A evidence]
	To reduce MACE and improve exercise performance [class I, level A evidence]
Class IIa; level A	In patients with diffuse CAD who cannot be completely revascularized by CABG alone, adjunctive TMR + CABG can be recommended:
	To improve long-term angina relief [class IIa, level A evidence]
	To reduce 30-day mortality and MACE [class IIa, level A/B evidence]
	To improve 1-year exercise performance [class IIa, level A evidence]
Class IIa; level B	In stable patients with refractory severe angina not amenable to conventional revascularization, TMR can be recommended instead of MMT alone:
	To reduce readmissions and re-interventions [class IIa, level B evidence]

studies may have contributed to heterogeneity among the outcomes.

Finally, the lack of sufficient numbers of randomized trials to inform every detail of this consensus statement is an inherent limitation that deserves discussion here. Although this limitation is common for all consensus statements,[9,26,27] it is also true for all decisions in medicine and it does not provide justification to discount the consensus statement. Rather, the purpose of consensus statements that are evidence-based is to explicitly define the best available evidence to inform each statement so that clinical and resource-related decision-making can be optimally evidence-based. This will facilitate better decision making than if decisions were made without objective consideration of all of the evidence. The labels on the statements identify when greater assurance [level A] or lesser certainty [level B] can be given to the statement, and helps to direct the amount of effort that should be given to implementing the recommendations.

Feasibility and Training

Judgments about whether the costs and resources required to provide TMR are necessarily dependent on the local context and setting. Studies to date have not addressed whether the time, skills, staff, training and equipment necessary to carry out the recommendations, and the ability of health care systems to implement them. Specific barriers to implementing the TMR as an option for patients with refractory angina to achieve the recommendations given by this consensus conference were not explicitly discussed, due to the broad range of global contexts represented by the consensus panel and the necessity for customization within local considerations. Issues to consider when localizing these recommendations to specific settings include ensuring adequate training and skills certification for TMR, purchasing laser equipment along with supporting technologies and maintaining its integrity, and ensuring reassessment of skills and techniques against the progression of the evidence over time.

Future Directions

The consensus statements presented here will need to be updated when new evidence becomes available, or if there are important changes in the available laser technologies or associated techniques. This is especially important for this consensus statement, given that the evidence base is relatively small. Research efforts should be encouraged to address the gaps in the evidence as outlined in the statement for further research given above.

Summary and Conclusions

After review and discussion of the best available evidence, the following summary consensus recommendations were delineated (Table 3):

In stable patients with refractory severe angina not amenable to conventional revascularization, TMR can be recommended instead of MMT alone:

- To improve sustained angina relief [class I, level A evidence]
- To reduce MACE and improve exercise performance [class I, level A evidence]

- To reduce readmissions and reinterventions [class IIa, level B evidence].
- 1. In patients with diffuse CAD who cannot be completely revascularized by CABG alone, adjunctive TMR + CABG can be recommended:
- To improve long term angina relief [class IIa, level A evidence]
- To reduce 30-day mortality and MACE [class IIa, level A/B evidence]
- To improve 1-year exercise performance [class IIa, level A evidence].

Given these statements, it was the prevailing opinion of the consensus panel members that TMR represents a viable alternative to conventional maximal medical management for patients with refractory stable angina not amenable to conventional surgical revascularization [class I, level B].

Adjunctive TMR + CABG can be considered a part of the therapeutic armamentarium in chronic stable angina patients with coronary morphology deemed only partially amenable to revascularization by conventional surgical revascularization [class IIa, level B].

Future research efforts should address the role of TMR relative to or in combination with novel biological treatments.

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