Transmyocardial laser revascularisation. Clinical experience in patients with refractory angina pectoris
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Transmyocardial laser revascularisation:
A review of clinical literature

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Chapter 7

Abstract

Since its first clinical application in 1981, many reports have described the use of TMLR as a treatment for refractory angina pectoris. In the current chapter both uncontrolled and controlled stand-alone TMLR studies (using CO₂, Ho:YAG and XeCl excimer lasers) that have been published are reviewed.

For uncontrolled TMLR, a total of 721 CO₂, 251 Ho:YAG and 34 XeCl excimer patients have been described. Overall, in respectively 349, 222 and 27 patients with a completed one-year follow up, angina decreased from class 3.2 ± 0.5 to 2.2 ± 0.9 after CO₂, 3.7 ± 0.3 to 2.0 ± 0.7 after Ho:YAG and 3.5 ± 0.5 to 1.8 ± 0.5 after XeCl excimer TMLR. Mortality at 8-12 months was 25% after CO₂ TMLR, 12% after Ho:YAG TMLR and 7% after XeCl excimer TMLR.

In six randomised TMLR trials (3 CO₂, 2 Ho:YAG, 1 XeCl excimer), angina decreased ≥ 2 classes in 24-72% of CO₂ treated patients, in 61-76% of Ho:YAG treated patients and in 79% of XeCl excimer treated patients (all significant compared to medication). Including cross-over, one-year mortality was 12-21% after CO₂, 5-13% after Ho:YAG TMLR and 7% after XeCl excimer TMLR (no differences compared to medication).

A meta-analysis of the six randomised TMLR trials was also performed. In a total of 967 patients, 57.1% (197 out of 345) of the TMLR patients improved ≥ 2 classes in angina compared to 14.2% (40 out of 282) in the maximal medication group (absolute difference 42.9%, 95%CI: 35%-51%, p < 0.0001). The relative risk of mortality was 1.16 (95%CI: 0.80-1.71, p = 0.43) comparing TMLR with maximal medication.

In conclusion, all studies with the three clinically used lasers demonstrate relief of angina in the majority of patients, combined with an acceptable peri-operative mortality. Therefore, after a proper selection of patients, TMLR can be performed safely and effectively and should be the treatment of choice in selected patients. Clinically, as there was no important difference between the three types of laser, currently any of these lasers is suitable for TMLR.
Introduction

Transmyocardial laser revascularisation (TMLR) is a treatment option for refractory angina pectoris. Three different laser types are currently in clinical use: A high power CO₂ laser (wavelength 10.6 µm), a Ho:YAG laser (2.12 µm) and a XeCl excimer laser (308 nm). Significant clinical improvement has been shown in randomised clinical trials using CO₂ or Ho:YAG lasers. Currently, our own work is available (chapters 5 and 6) but no other randomised trials have been published on excimer TMLR. However, clinical improvement has been demonstrated after XeCl excimer TMLR in several uncontrolled studies [93,110,111]. In this review, both the uncontrolled and controlled clinical literature on TMLR is described and discussed, with a focus on its effect on peri-operative mortality, and on angina and mortality during the first year and at long-term follow up.

Methods

Data acquisition and selection
In this review, books, journal articles, reviews and (meeting) abstracts reporting on clinical work are included. The literature acquisition was performed using PubMed: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) and the ‘all years’ database from the Web of Science (http://wos.library.tudelft.nl/CIW.cgi). The following keywords were used in the searches (both in American and Oxford English): transmyocardial laser revascularisation, laser myocardial revascularisation, transmyocardial revascularisation, direct myocardial revascularisation, percutaneous laser revascularisation, percutaneous myocardial laser revascularisation, percutaneous myocardial revascularisation, TMLR, TMR, PMR and DMR.

As we aim to give a clinical overview of TMLR, we have only considered reports on stand-alone TMLR and we have disregarded studies on TMLR as an adjunct to CABG or studies where results of stand-alone TMLR and TMLR as an adjunct to CABG were lumped together and could not be separated (as was, unfortunately, done in an international registry of 932 patients [131]). In the literature, methods to describe the effect of TMLR on angina are diverse. Both the classification of the CCS and the NYHA are used. Unless stated otherwise, this report considers CCS functional angina classes. Furthermore, some colleagues report on the change in mean angina class, some on the number or percentage of patients that are classified in 1 (or 2) angina classes at baseline and follow up (for
instance: 93% of the patients were in class III or IV at baseline), some only
give the number or percentage of patients with a decrease of angina of
≥ 2 classes and / or ≥ 1 class, and others give only graphs or figures. To
enable comparison of the various reports with respect to angina, we
calculated the mean angina class at baseline and follow up for each study.
If results were given for two classes [132], we assumed an even
distribution over the classes. If the sum of the surviving and non-surviving
patients at follow up is lower than the number of patients at baseline,
patients did not yet reach follow up at the time of the report or were lost to
follow up. Numbers for the latter two are not reported separately in this
review. For overall calculations we disregarded reports where the mean
angina class or mortality could not be derived. Furthermore, we
disregarded results of earlier reports of groups that later, individually or as
a multi-centre study, reported on a larger number of patients with a longer
follow up, assuming that the later report included patients of the earlier
report(s). Overall results are calculated by considering the weighted results
of each study.

Meta-analysis
To perform a statistical overview of randomised studies (refs [71-77] and
chapters 5 and 6), standard methods for combining information from 2 x 2
tables were used [133]. For each trial, 2 x 2 tables were constructed for the
numbers of TMLR-treated patients and controls (treated with maximal
medication) who experienced the endpoint under consideration. Absolute
differences and relative risks (RR’s) were calculated in such a way that
benefit from TMLR was associated with a RR less than 1 or an absolute
difference greater than zero. Overall event rates were calculated as
weighted averages of the trial-specific rates with weights proportional to
the total sample sizes of the trials. The overall point estimates for RR was
calculated using the Mantel-Haenszel estimate [134]. The corresponding
95% confidence intervals (95%CI) were calculated by the test-based
method using the Mantel-Haenszel chi-square statistic [134].

Results

Uncontrolled TMLR studies
Uncontrolled CO₂ TMLR
TMLR was pioneered by Mirhoseini et al., who first used clinical CO₂
TMLR as an adjunct to CABG in areas that could not be revascularised by
Review clinical TMLR

grafts [68]. Following this report, Okada et al. reported the first successful clinical stand-alone CO_{2} TMLR procedure in 1986 [135]. Then, in 1990, a higher power CO_{2} laser (*Heart Laser, PLC Medical Systems, Franklin, MA, USA*) became available, and made it possible to perform TMLR on the beating heart. Since then, more than 15 reports have been published on uncontrolled stand-alone CO_{2} TMLR (as well as three randomised clinical trials comparing CO_{2} TMLR with maximal medication). In an attempt to assess the overall results on anginal relief and mortality of published uncontrolled studies on stand-alone TMLR we considered all patients of these reports [132,136-143] and disregarded reports according to the criteria described in the methods section [94,95,144-149]. Overall, for a total of 721 stand-alone CO_{2} TMLR patients anginal status has been described in uncontrolled studies. Of these 721 patients, 349 patients had a follow up of 12 months. Angina decreased from class 3.2 ± 0.5 at baseline to 2.2 ± 0.9 at 12 months follow up. Overall, peri-operative mortality was reported for 591 patients of which 60 died (10%) and mortality at 12 months was 25% (114 out of 463 patients).

For one uncontrolled trial, long-term follow up to 7.2 years after CO_{2} TMLR has been reported (Horvath et al. [109]). Because of its importance, this study is discussed separately. From the original 195 patients that were included in a Phase II and III USA FDA trial, 82 had died (41 in the first year, overall mortality 42%), 33 underwent an additional revascularisation procedure (16 in the first year, overall 17%) and 2 (1%) were lost to follow up. The remaining 78 patients, who received their TMLR procedure 5 years earlier, had baseline angina class 3.7 ± 0.4 and at 12 months follow up this was 1.5 ± 1.1. Furthermore, 60 patients (77%) showed ≥ 2 angina classes relief and 69 patients (89%) ≥ 1 angina class. At an average of 5 years follow up, angina class was 1.6 ± 1.1, and 53 patients (68%) and 71 patients (91%) showed a relief of ≥ 2 and ≥ 1 angina class respectively.

Uncontrolled Ho:YAG TMLR

The Ho:YAG laser is the second most used laser (after the CO_{2} laser) for TMLR. Dowling et al. assessed the efficacy of Ho:YAG TMLR (*TMR 2000, Eclipse Surgical Technologies, Sunnyvale, CA, USA*) to relieve refractory angina in 85 patients. Symptomatic improvement was excellent, with angina class improving from 4.0 ± 0 at baseline to 2.3 ± 0.7 at 3 months follow up. At 1 month follow up 10 patients had died (mortality of 12%) [150]. Milano et al. [151] performed Ho:YAG TMLR in 16 patients using the same laser and settings as Dowling et al.. Angina
decreased from $3.4 \pm 0.5$ at baseline to $1.8 \pm 0.7$ at 12 months follow up. Two patients died during follow up (mortality of 13%).

De Carlo et al. [152] have assessed Ho:YAG TMLR efficacy in 34 patients using the same laser and settings as Dowling et al., and included the 16 patients described earlier by Milano et al.. Angina decreased from class $3.6 \pm 0.5$ at baseline to $1.8 \pm 0.8$ at 12 months follow up. Five out of 34 patients had died at 12 months follow up (mortality 15%).

Sundt et al. reported on two groups of patients treated with a different Ho:YAG laser (NSLX-6, CardioGenesis Corp., Sunnyvale, CA, USA). One series included 49 patients who received Ho:YAG TMLR at one of 10 sites in the United States or Europe. Data at 3 months were available for only 24 patients, all of who had class III or IV angina at baseline (assumed mean angina class $3.5 \pm 0.5$). Given the reported decrease in angina, this was approximately class $1.7 \pm 0.7$ both at 3 and 6 months follow up ($n = 14$). There were 3 peri-operative deaths in this series (mortality of 6%) [153]. Another series, which included 19 patients, showed similar results with a decrease in angina from class $3.5 \pm 0.5$ at baseline to $1.9 \pm 1.0$ in 17 patients with a completed 12 months follow up [154]. Mortality was not reported for this series.

Diegeler et al. applied stand-alone Ho:YAG TMLR using the same laser and settings as Sundt et al. and created $26 \pm 6$ channels per patient in 16 patients [155]. Unfortunately, part of the results is given for a group of patients that includes results of patients treated by TMLR as an adjunct to CABG (e.g. the reported follow up is for 23 patients instead of 16). As a result, only limited data were available for stand-alone Ho:YAG TMLR.

Schneider et al. [156] reported long-term follow up in 14 patients, probably the same 14 that were earlier described by Diegeler et al. [155]. After an initial significant decrease of angina from $3.5 \pm 0.5$ at baseline to $1.6 \pm 0.7$ and $1.7 \pm 0.5$ at 12 and 18 months respectively, angina was slightly increased at 2 and 3 years follow up, to $2.4 \pm 1.0$ and $2.5 \pm 1.2$ respectively (non-significant relief of angina compared to baseline).

Finally, Guleserian et al. and Muxi et al. reported on quality of life and MiBG SPECT scintigraphy, respectively, after Ho:YAG TMLR using the same laser as Dowling et al. [150]. In these papers, data on peri-operative and one-year mortality were included [88,157]. Guleserian et al. included 34 patients, of which 3 died peri-operatively (9%). One-year follow up was complete in 27 patients (one-year mortality 9%) [157]. Muxi et al.
observed a one-year mortality in 1 out of 16 patients (6%) and no peri-operative deaths [88].

Overall, disregarding early results of the groups of Milano and De Carlo [151] and of Diegeler and Schneider [155], a total of 251 Ho:YAG TMLR patients have been described in uncontrolled studies. Of these 251 patients, 108 patients had a mean follow up of 8 ± 4 months and angina decreased from class 3.7 ± 0.3 at baseline to 2.0 ± 0.7 at follow up. Overall mortality was 27 out of 222 patients (12%) at 8-12 months follow up.

Uncontrolled XeCl excimer TMLR
The first XeCl excimer TMLR treatments were performed as adjuncts to CABG. Krabatsch et al. reported on 19 patients [158], Morgan and Campanella followed with a report on 30 patients [159] and Klein et al. with results in 98 patients [93]. Besides their experience with XeCl excimer TMLR as an adjunct to CABG, Klein et al. also assessed the efficacy of stand-alone XeCl excimer TMLR in 12 patients [93]. They used a 1 mm diameter fibre in combination with a (non-ECG triggered) Medolas MAX-20 XeCl excimer laser (Medolas, Munich, Germany) at 40 mJ/pulse and a repetition frequency of 40 Hz. A mean of 33 channels/patient were created in ~110 pulses/channel. Overall, angina reduced from 3.7 at baseline (n = 12) to 1.5 (n = 11) and 2.3 (n = 8) at 3 months and 12 months follow up respectively (for NYHA functional class these results were 3.1, 1.8 and 2.6 respectively). None of the 12 patients died during follow up.

Lee et al. [110] performed XeCl excimer TMLR in 15 patients, and they assessed its effect on angina. Furthermore, MPS (201thallium SPECT), exercise tolerance testing and 24-hour ECG monitoring were assessed. A 600 µm diameter fibre was used in combination with a (non-ECG triggered) XeCl excimer laser at 9 mJ/pulse, a pulse duration of 40 ns and a repetition frequency of 240 Hz (Acculase Inc., San Diego, CA, USA). During TMLR 41 ± 16 channels were created per patient (range 24-61 channels). Two patients had died at 12 months follow up (mortality of 13%) and one patient was lost to follow up. In the remaining 12 patients angina reduced from class 3.5 ± 0.5 to 1.8 ± 0.8 at 12 months follow up. Nitroglycerin requirements were significantly decreased and exercise tolerance was non-significantly increased by 22% at 12 months follow up. 24-Hour ECG monitoring showed no increase of arrhythmias over baseline values. No results were given with regard to an effect of TMLR on myocardial perfusion.
In 7 patients, Kavanagh et al. [111] assessed the efficacy of XeCl excimer TMLR (using the same laser and settings as Lee et al.). During TMLR 69 ± 5 channels were created per patient (range 56-90 channels). Angina decreased from pre-operative class III to class I in 6 patients and to class II in the one remaining patient at 12 months follow up. Overall, exercise time increased with 63% at 6 months follow up (only two measurements available at 12 months follow up) and perfusion as assessed with MPS (rest $^{201}$thallium and stress $^{99m}$technetium sestamibi SPECT) showed increased perfusion at 12 months follow up. However, changes in perfusion were discordant with the clinical results: The highest increase in perfusion was found in the patient with the least clinical benefit (class II at 12 months follow up) and 2 other patients showed a decreased perfusion whilst their angina was decreased by two classes at 12 months follow up.

Overall, a total of 34 XeCl excimer TMLR patients have been described in uncontrolled studies. Angina decreased from class 3.5 ± 0.5 at baseline to 1.7 ± 0.5 at a mean follow up of 9 ± 4 months (n = 30) and 1.8 ± 0.5 at 12 months follow up (n = 27). At 12 months follow up, overall mortality was 7% (2 out of 29 patients).

All uncontrolled studies on excimer TMLR conclude that excimer TMLR is well tolerated, safe and effective in relieving angina.

**Randomised clinical trials**

*One-year results of randomised trials: General overview and meta-analysis*

The first randomised (multi-centre) trial was reported by March [71], followed by a (single-centre) randomised trial by Schofield et al. [75]. These studies, using the high power CO$_2$ laser manufactured by PLC Medical Systems (Heart Laser, PLC Medical Systems, Franklin, MA, USA) were followed by the first (multi-centre) randomised trial using a Ho:YAG laser ($NSLX-6$, CardioGenesis Corp., Sunnyvale, CA, USA) by Burkhoff et al. [73]. Frazier et al. [74] then published results of a randomised trial on a cohort that was also described by March [71]. The second (multi-centre) randomised trial using a Ho:YAG laser ($TMR 2000$, Eclipse Surgical Technologies, Sunnyvale, CA, USA) was published by Allen et al. [72] and was followed by a third (single-centre) randomised trial using the PLC CO$_2$ laser by Aaberge et al. [76]. Spertus et al. [77] published the QOL results of the patients described by Frazier et al. [74]. Finally, van der Sloot et al. reported on a single centre-trial using a XeCl excimer laser (chapter 5) and Huikeshoven et al. reported on the QOL of this study (chapter 6).
Table 1 shows the 12 months results of the randomised clinical trials. Overall, angina decreased \( \geq 2 \) classes in 24-79% of the TMLR patients (24-72% in the \( \text{CO}_2 \) trials, 61-76% in the Ho:YAG trials and 79% in the excimer trial, all significant compared to medication) and \( \geq 1 \) angina class in at least 63% of the TMLR patients. Of a total of 967 patients included in the six studies, the total one-year mortality after TMLR was 12.1% when excluding cross-over patients (56 out of 461 patients) and 13.4% (75 out of 560 patients) when including cross-over patients with one-year follow up after TMLR, versus 9.2% (34 out of 370 patients) receiving continued medication. Including cross-over patients, one-year mortality after TMLR was 5-21% (range 12-21% for \( \text{CO}_2 \), 5-13% for Ho:YAG and 7% for excimer) vs. 0-26% in the medication groups (excluding cross-over patients; 4-26% for \( \text{CO}_2 \), 10-12% for Ho:YAG and 0% for excimer). Overall, and in each separate study, no differences were found in mortality between TMLR and medications groups. Four out of six studies reported on quality of life (QOL) and all four showed a significant improvement [72-74]. Furthermore, three studies showed a significant increase in exercise tolerance [72-74] and only one study a significant increase in myocardial perfusion [74]. Overall, in five of the randomised studies TMLR was recommended (refs [72-74,76] and chapters 5 and 6) and in one study TMLR was not advocated because of a (not-significantly) higher mortality in the TMLR group [75].

Tables 2a-b show the event rates in the two treatment arms of the six trials comparing TMLR with maximal medication.

**Long-term result of one randomised trial**

Currently, long-term follow up of only one randomised clinical trial is available. Recently, Aaberge et al. published the long-term follow up [160] of patients included in the randomised trial in which \( \text{CO}_2 \) TMLR was compared to maximal medical treatment (one-year results in [76]). At a mean follow up of 43 months (range 32-60), the total mortality was 23% (including the 4% peri-operative mortality) and was not different between the groups. The significant initial improvement in angina symptoms persisted until 3 to 5 years after TMLR (improvement \( \geq 2 \) NYHA classes in 24% in the TMLR group compared to 3% in the medical treatment group). Anti-anginal medication was however not significantly reduced compared to the medication group. Compared to the initial report, they now added the effect of TMLR on QOL. Measured with the MOS SF-36, there were significant improvements in the physical health domains and the
physical component scale after TMLR, whereas the mental and social domains and mental component scale did not change significantly at 12 month follow up. Long-term effects on QOL were not given in this report.

<table>
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<tbody>
<tr>
<td>CO₂</td>
<td>Ho:YAG</td>
<td>CO₂</td>
<td>Ho:YAG</td>
<td>CO₂</td>
<td>XeCl excimer</td>
<td></td>
</tr>
<tr>
<td>power / pulse</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>6-8 W</td>
<td>1 kW</td>
<td>336-363 kW</td>
</tr>
<tr>
<td>pulse duration</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>30-50 ms</td>
<td>110 ns</td>
<td></td>
</tr>
<tr>
<td>energy / pulse</td>
<td>25 - 60 J</td>
<td>n.s.</td>
<td>21 - 57 J</td>
<td>30-50 J</td>
<td>37 - 40 mJ</td>
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<tr>
<td>beam / fibre diameter</td>
<td>1 mm</td>
<td>n.s.</td>
<td>1 mm</td>
<td>1 mm</td>
<td>1 mm</td>
<td></td>
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<tr>
<td># pulses / channel</td>
<td>1</td>
<td>n.s.</td>
<td>1</td>
<td>1</td>
<td>12 - 20</td>
<td></td>
</tr>
<tr>
<td># of channels / pt</td>
<td>6-75 (30)</td>
<td>9-42 (18)</td>
<td>37±13 vs 36±13 vs. n.r.</td>
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</tbody>
</table>

Table 1. Results of six randomised studies. MET = metabolic equivalents (test not performed at baseline); Med = medication; n = number of patients; n.p. = not performed; n.r. = not reported; n.s. = not specified; pt(s) = patient(s); SDS = summed difference score; * = p < 0.001 compared to control; † = p < 0.01 compared to control; ‡ = p < 0.05 compared to control; # = number; § = results are mean ± standard deviation or range (median); §§ the NYHA classification was used in the studies by Aaberge et al. and van der Sloot et al., the other four studies used the CCS classification; " = percentage of patients with improved perfusion.

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Decrease of angina with ≥ 2 classes (%)</th>
<th>Absolute difference (95%CI)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>TMLR vs. maximal medication</td>
<td></td>
</tr>
<tr>
<td>March/Frazier/Sportus</td>
<td>192</td>
<td>44/61 (72%) *</td>
<td>13/20 (65%) *</td>
</tr>
<tr>
<td>Schofield et al.</td>
<td>188</td>
<td>18/74 (24%)</td>
<td>3/78 (4%)</td>
</tr>
<tr>
<td>Burkhoff et al.</td>
<td>182</td>
<td>47/77 (61%)</td>
<td>8/73 (11%)</td>
</tr>
<tr>
<td>Allen et al.</td>
<td>275</td>
<td>58/76 (76%) *</td>
<td>16/50 (32%) *</td>
</tr>
<tr>
<td>Aaberge et al.</td>
<td>100</td>
<td>19/43 (44%)</td>
<td>0/46 (0%)</td>
</tr>
<tr>
<td>van der Sloot et al.</td>
<td>30</td>
<td>11/14 (79%)</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>Overall</td>
<td>967</td>
<td>197/345 (57.1%) *</td>
<td>40/282 (14.2%) *</td>
</tr>
</tbody>
</table>

Table 2a. Decrease of angina with ≥ 2 classes in six randomised studies of TMLR vs. maximal medication. n = total number of included patients; 95%CI = 95% confidence interval; * = p < 0.0001 compared to maximal medication; * = cross-over excluded; † = Mantel-Haenszel’s method.
Review clinical TMLR

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Mortality (%)</th>
<th>Relative risk (95%CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TMLR</td>
<td>maximal medication</td>
</tr>
<tr>
<td>March/Frazier:Spertus</td>
<td>192</td>
<td>28/132 (21%)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>7/27 (26%)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Schofield et al.</td>
<td>188</td>
<td>11/93 (12%)</td>
<td>4/91 (4%)</td>
</tr>
<tr>
<td>Burkhoff et al.</td>
<td>182</td>
<td>5/92 (5%)</td>
<td>9/90 (10%)</td>
</tr>
<tr>
<td>Allen et al.</td>
<td>275</td>
<td>24/178 (13%)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>12/97 (12%)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aaberge et al.</td>
<td>100</td>
<td>6/50 (12%)</td>
<td>4/50 (8%)</td>
</tr>
<tr>
<td>van der Sloot et al.</td>
<td>30</td>
<td>1/15 (7%)</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>967</td>
<td>75/560 (13.4%)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>34/370 (9.2%)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Table 2b. Mortality in six randomised studies of TMLR vs. maximal medication. n = total number of included patients; 95%CI = 95% confidence interval; " p = 0.43 compared to maximal medication; "<sup>**</sup> = cross-over excluded; "<sup>-</sup> = cross-over with completed one-year follow up after TMLR included; "<sup>1</sup> = Mantel-Haenszel’s method.

Discussion

CO₂, Ho:YAG and excimer TMLR results in formation of channels with a particular shape and diameter and with varying degrees of myocardial thermal and mechanical damage. However, whatever the working mechanism of TMLR may be, differences in laser-tissue interaction seem to translate into only small differences in therapeutic efficacy, if any, since in all randomised CO₂ or Ho:YAG laser trials [71-77] and in uncontrolled excimer laser studies [93,110,111] TMLR was effective in relieving angina. Furthermore, in all studies that assessed QOL an improvement was demonstrated. Schneider et al. recently reported for a limited number of patients (n = 14) that at 2 and 3 year after Ho:YAG TMLR the earlier reduction of angina did not sustain [156]. However, the studies with the longest follow up (5 years) demonstrated that in patients treated with Ho:YAG or CO₂ TMLR a reduction of anginal pain (and an improvement in quality of life) can be maintained for many years [109,160].

Five out of six randomised trials (refs [71-74,76,77] and chapter 5) conclude that TMLR results in a relief of angina, especially in patients with class IV angina. The studies by March, Frazier et al. and Spertus et al., that all more or less describe the same cohort of patients [71,74,77], and that by Allen et al. [72], included cross-over for patients who failed medical therapy. The cross-over rates were 32% and 60% respectively. We consider the design with cross-over an important drawback of these studies. On the other hand, the choice of Allen et al. to exclusively include patients with class IV angina has increased the value of this study. It is noteworthy that in all six randomised studies, the patient groups that received TMLR directly after randomisation had a peri-operative mortality of 1-7%, while the cross-over patients, initially randomised to medical therapy, had a peri-
operative mortality of 9%. When combining the results of the controlled / randomised studies with those of the uncontrolled reports, overall mortality up to 12 months follow up was 22% (159 out of 738 patients) after CO_2 TMLR, 11% (56 out of 492 patients) after Ho:YAG TMLR, 7% (3 out of 44) after XeCl excimer TMLR and 17% (218 out of 1274 patients) for the three lasers combined (i.e. all reported TMLR patients with completed one-year follow up).

Only one report of a randomised clinical trial has refrained from concluding that TMLR should be used in a selected group of patients. This study, by Schofield et al. [75], is the second published controlled trial comparing the efficacy of TMLR with medical management and therefore it is of great value and had a high impact. However, in our opinion the authors’ conclusion that “the adaptation of TMLR cannot be advocated” is not warranted for several reasons. First, the negative conclusion is based on a non-significant difference (p = 0.14) in one-year survival between the TMLR and medical-management group (89% vs. 96%). One-year survival in the TMLR group (consisting mainly of patients with a history of coronary artery bypass grafting) was however comparable with one-year survival (86%) after elective re-operation for coronary bypass surgery in similar patients [161]. Therefore, in our opinion the reported survival after TMLR is acceptable. Furthermore, angina score decreased by ≥ 2 classes in 24% of TMLR and 4% of medical-management patients at one-year (p < 0.001). Although this is lower than in the other randomised trials, it is interesting to note that compared to the other trials relatively few patients (25 out of 94 patients or 27% in both groups) had class IV angina at baseline. As a result, clinical efficacy, defined as a decrease in angina of ≥ 2 classes, a priori could be expected to be low. Detailed analysis of the publication shows a decrease of ≥ 1 class in at least 66% of the TMLR patients and only in 9% of medical-management patients at 3 months. We would like to emphasise that these results are excellent considering the fact that these patients had predominantly class III angina, were severely ill with inoperable coronary artery disease and probably had a poor quality of life. Second, in our opinion improved quality of life is the most important goal of treatment in these patients. Although Schofield et al. mention that quality of life was investigated, unfortunately the outcome of this endpoint has (still) not been not reported. Quality of life was also assessed in other randomised trials discussed above and in all these trials it was significantly better after TMLR than medical management. In conclusion, the interesting data presented by Schofield et al. show a significant relief of angina in
patients, while mortality was not significantly increased by TMLR. Therefore, in our opinion no negative conclusions on effectiveness of TMLR can be drawn from these results.

Conclusion

In conclusion, all studies with the three clinically used lasers demonstrate that TMLR results in relief of angina (and improvement of quality of life) in the majority of patients. Improved perfusion has been demonstrated in only one out of six randomised clinical trials and in only a few uncontrolled studies. Consequently, TMLR seems to be a primarily symptomatic treatment. However, the label ‘experimental’ that many clinicians still use for TMLR does not do justice to the outcome of the randomised trials. After a proper selection of patients, TMLR can be performed safely and effectively with a low peri-operative mortality and morbidity and a high success rate that can sustain for a period of years [109]. Given these results, the conclusion is warranted that CO₂, Ho:YAG or XeCl excimer TMLR should be the treatment of choice in selected patients. Clinically, as there was no important difference between the three types of laser, currently any of these lasers is suitable for TMLR.