A meta-analysis of randomized control trials comparing minimally invasive direct coronary bypass grafting versus percutaneous coronary intervention for stenosis of the proximal left anterior descending artery

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Summary

Percutaneous intervention (PCI) and minimally invasive direct coronary bypass grafting (MIDCAB) are both well-accepted treatment options for isolated high-grade stenosis of proximal left anterior descending coronary artery. Small studies comparing the two modalities have yielded conflicting results. We performed a meta-analysis of randomized control trials to compare percutaneous intervention with minimally invasive coronary bypass grafting for isolated proximal left anterior descending artery stenosis. Five randomized trials with a total of 711 patients and average follow-up of 2.3 years were included in the analysis; 380 patients received stents and 331 underwent surgery. Only one trial used drug eluting stents. There were a small number of events overall in each trial. Difference between mortality was 12 events versus 15 between the PCI versus MIDCAB group. Similarly, the difference in myocardial infarction was 14 versus 10, and target vessel revascularization was 56 versus 19. The relative risk for stenting versus MIDCAB was 0.96 [95% CI: 0.47, 1.99], for mortality and myocardial infarction, 0.77 [95% CI: 0.30, 2.01], p = 0.60, $I^2 = 10.4\%$ for mortality and 1.81 [95% CI: 0.80, 4.06], p = 0.15, $I^2 = 65.9\%$ for the composite end point of mortality, myocardial infarction and target vessel revascularization. Excluding the trial with drug eluting stents the relative risk for the composite outcome of mortality, myocardial infarction and target vessel revascularization was significantly higher for PCI [RR = 2.27 (95% CI: 1.32, 3.90), p = 0.003, $I^2 = 18.9\%$]. Overall mortality and myocardial infarction rates are similar for bare metal stents versus MIDCAB, but surgery was associated with significantly lower rates of repeat revascularization. The number of randomized patients and events were small. The effect of drug eluting stents might close the gap of repeat revascularization compared to MIDCAB for this disease.

Keywords: LAD stenosis; Percutaneous coronary Intervention; Minimally Invasive bypass grafting; Outcome

1. Introduction

Myocardial revascularization has become the cornerstone of management of coronary artery disease (CAD) with interventional treatment generally accepted for proximal stenosis of left anterior descending coronary artery (LAD). The prognosis of patients with untreated high-grade proximal stenosis of the left anterior descending coronary artery is poor [1–5]. Despite advancement in medical therapy contemporary studies comparing medical treatment and revascularization for this lesion still recommend revascularization to decrease rates of cardiac death and acute myocardial infarction [6]. For these patients the two well-established treatment procedures are percutaneous coronary intervention (PCI) and conventional coronary artery bypass grafting (CABG) (grafting the left internal mammary artery to LAD). Both procedures are more effective than medical therapy for relieving symptoms, and CABG improves survival in certain subsets of patients [5,7–9]. Studies have also shown CABG to be more effective in relieving anginal symptoms, although it is associated with significant initial morbidity. This benefit is largely because of subsequent protection of the entire proximal and mid-LAD from future disease progression as opposed to focal treatment with stent with PCI. The ARTS trial, however, compared CABG with stenting for multivessel coronary artery disease and showed no difference in myocardial infarction or mortality at 5 years [10]. In recent years, minimally invasive direct coronary artery bypass (MIDCAB) has been used for treating patients with proximal stenosis of LAD [11,12]. This operation involves a small left anterior thoracotomy and Anastomosis of internal mammary artery to LAD by direct suture. It is performed on a beating heart with the use of stabilizing devices or using a minimal access bypass system with endo-aortic clamping and cardioplegic arrest [13]. It enables a shorter hospital stay with lower
postoperative complications and better quality of life with similar safety and long-term efficacy as conventional CABG [14,15]. Some studies have raised concern that MIDCAB has a slightly higher prevalence of peri-procedural adverse events as compared to PCI [4] and that the success rate of MIDCAB is slightly higher prevalence of peri-procedural adverse events as compared to PCI [4] and that the success rate of MIDCAB.

Reeves et al. 1999—2001 United Kingdom 100 Mortality, MI, TVR and angina pectoris class 1
Hong et al. 3/2003—11/2003 Korea 189 Cardiac Mortality, MI and TVR 0.5
Drenth et al. 1997—1999 Italy 102 Mortality, MI, stroke and TVR 2.9
Thiele et al. 1997—2001 Germany 220 Mortality, MI and TVR 5.6
Cisowski et al. 2000—2001 Poland 100 Mortality, MI and TVR 1.0

| Study          | Years           | Location | No. of patients | Primary end point                  | Follow-up (years) |
|----------------|-----------------|----------|-----------------|------------------------------------|-------------------|
| Cisowski et al. | 2000—2001       | Poland   | 100             | Mortality, MI and TVR              | 1.0               |
| Thiele et al.   | 1997—2001       | Germany  | 220             | Mortality, MI and TVR              | 5.6               |
| Drenth et al.   | 1997—1999       | Italy    | 102             | Mortality, MI, stroke and TVR      | 2.9               |
| Hong et al.     | 3/2003—11/2003  | Korea    | 189             | Cardiac Mortality, MI and TVR      | 0.5               |
| Reeves et al.   | 1999—2001       | United Kingdom | 100         | Mortality, MI, TVR and angina pectoris class | 1               |

2. Methods

The primary aim of the systematic review of randomized trials was to compare the MIDCAB versus PCI for proximal stenosis of the left anterior descending artery. Two investigators identified all published randomized trials comparing PCI and MIDCAB, and assessed the eligibility of each trial. Trials were eligible for inclusion if patients prior to randomization were deemed suitable for both PCI and MIDCAB. The dichotomous end points from individual trials were analyzed using the relative risk (RR) as a parameter of efficacy with its 95% confidence interval (CI). The heterogeneity of the treatment effect between studies was evaluated using the $I^2$ statistic. A p-value of 0.05 or less was considered as low heterogeneity, 25—50% as moderate and greater then 75% as high heterogeneity. The summary estimators of treatment effect were calculated using the DerSimonian and Laird random-effect method. A $p$-value less then 25% were considered as low heterogeneity, 25—50% as moderate and greater then 75% as high heterogeneity. The summary estimators of treatment effect were calculated using the DerSimonian and Laird random-effect method. A $p$-value of 0.05 or less was considered as significant. The number of patients needed to be treated to prevent one end point was calculated for the end point using the overall weight risk difference [NNT = 1/(absolute risk difference)].

3. Results

A total of 306 citations were found in Medline. Several papers were excluded because of their nonexperimental design [3,16—19]. We finally identified six eligible randomized clinical trials, and complete articles were retrieved when applicable and checked for compliance to the inclusion and exclusion criteria [20—24]. We excluded one trial as only 10% of the study population underwent MIDCAB [25].

The five studies included in the final analysis randomized 711 patients, 380 to PCI and 331 to MIDCAB (Table 1). The mean age was 58 years. On average, males accounted for 72% and diabetics for 27% of subjects. Overall, a normal baseline...
left ventricular ejection fraction and absence of a recent acute coronary syndrome was a prerequisite for enrolment, thus leading to limited representation of very high risk patients. Only one trial compared drug eluting stents with MIDCAB. All patients in both groups received at least 100 mg of aspirin per day. Patients in the bare metal stent trials received either ticlopidine [20,21,23] or clopidogrel [24] after a loading dose the day before the procedure for 4 weeks. The trial utilizing DES [22] administered 300 mg of clopidogrel or 500 mg of ticlopidine on the day prior to the procedure and continued the medication for 6 months.

3.1. Outcomes

There were a small number of events overall in each trial. Difference between mortality was 12 events versus 15 between the PCI versus MIDCAB group. Similarly the difference in myocardial infarction was 14 versus 10, and target vessel revascularization was 56 versus 19. Myocardial infarction was not defined specifically in any of the trials except that of Reeves et al., who mentioned that their definition needed to be confirmed by electrocardiographic changes. Target vessel revascularization was undertaken for documented stenosis (50%). The was no difference in mortality between PCI (3.2%) and MIDCAB (4.5%) [RR = 0.77 (95% CI: 0.30, 2.01), p = 0.60, $I^2 = 10.4\%$, (Table 2) and similar was true for the combined end point of mortality (6.8%) and myocardial infarction (7.5%) [RR = 0.96 (95% CI: 0.47, 1.99), p = 0.92, $I^2 = 17.5\%$, (Table 3) and even the composite end point of mortality, myocardial infarction and target vessel revascularization in the PCI group (21.6%) compared to MIDCAB (13.3%) [RR = 1.81 (95% CI: 0.80, 4.06), p = 0.15, $I^2 = 65.9\%$, (Table 4). In view of the moderate heterogeneity we excluded the trial with drug eluting stents. This resulted in a significantly higher risk of MIDCAB in comparison to PCI for the composite outcome of mortality, myocardial infarction and target vessel revascularization [RR = 2.27 (95% CI: 1.32, 3.90), p = 0.003, $I^2 = 18.9\%$, (Table 5). The relative risk however remained non significant for the other outcomes. For the end point of mortality only, relative risk was 0.96 [(95% CI: 0.46, 2.03), p = 0.92 $I^2 = 0\%$] (not shown) and 0.95 [(95% CI: 0.53, 1.73), p = 0.88 $I^2 = 0\%$], for the end point of mortality and myocardial infarction. (Table 6).

PCI was associated with increased rates of repeat revascularization (50% for PCI vs 34% for MIDCAB). The absolute risk increase was 16% (95% CI 6.1—25.5%) translating into NNT of seven (95% CI 3.9—16.4) patients to avoid repeat revascularization with MIDCAB versus stenting in an average follow-up of 27 months. There was moderate heterogeneity when all trials were combined in the analysis; this decreased after the DES trial was excluded.

### Table 3
Comparison of PCI versus MIDCAB for the outcome of mortality and non-fatal myocardial infarction

| Study or sub-category | PCI nN | MIDCAB nN | RR (random) 95% CI | Weight % | RR (random) 95% CI |
|-----------------------|--------|-----------|-------------------|----------|-------------------|
| Crivti et al          | 1/50   | 0/50      |                   |          |                   |
| Dreith et al          | 0/51   | 0/51      |                   |          |                   |
| Thiele et al.         | 11/110 | 11/110    |                   |          |                   |
| Hong et al            | 9/119  | 2/70      |                   |          |                   |
| Reeves                | 0/50   | 2/50      |                   |          |                   |
| Total (95% CI)        | 100.00 | 100.00    |                   | 0.77     |                   |
| Total events: 26 (PCI), 25 (MIDCAB) | | | | | |
4. Discussion

The present meta-analysis of randomized trials comparing MIDCAB versus PCI for proximal LAD disease shows that PCI and MIDCAB have similar overall survival, myocardial infarction and repeat target vessel revascularization. PCI with bare metal stents is fraught with significantly increased risk of repeat revascularization in comparison to MIDCAB. This was evident when the composite end point favored MIDCAB after excluding the trial that used DES stent.

The LAD coronary artery usually supplies the largest myocardial territory compared to other epicardial coronary arteries [26]. Patients with stenosis at proximal LAD are at higher risk than those with lesions at other locations with...
untreated lesions having poor prognosis [2]. PCI initially appears more attractive to the patient as it is less invasive, requires shorter hospital stay, and is usually associated with less acute morbidity compared to surgery. The challenge here is the high rate of restenosis ranging from 29 to 44% for bare metal stents [4,21,27]. The development of drug eluting stents has been shown to decrease the rates of restenosis; however, only one randomized trial included in our meta-analysis used drug eluting stents. Other factors affecting rates of restenosis include diabetes (on average 27% of our subjects had diabetes), lesion length, and small vessel diameter [28]. These data are variably reported (Table 7) with mean stent length being 18.8 mm and mean LAD reference diameter 2.8 mm in our analysis, but this might also affect the results of surgery as there were no statistically significant differences between the lesions treated with MIDCAB versus PCI. Other strategies to decrease rates of revascularization such as glycoprotein 2b/3a inhibitors were not used in any of these trials. The [29] Type B/C lesions were >50% of the lesions in this study. These are known to have higher rates of restenosis; therefore, as previously suggested there might be a possible role for predictive restenosis risk models to identify patients who will benefit from surgery compared with stenting [30,31].

Treatment of isolated stenosis of the left anterior descending coronary artery through a left anterior thoracotomy has been advocated as an acceptable alternative to standard coronary artery bypass. The main concern about MIDCAB surgery has been the quality of coronary anastomoses due to the necessity to perform anastomoses on a beating heart with a small thoracotomy, and temporarily occluded coronary artery. Studies have demonstrated that MIDCAB appears to give a good anastomotic patency, relief of symptoms and long-lasting results based on the known longevity of internal thoracic artery grafting after conventional CABG surgery [12]. In one trial the learning curve was demonstrated by a patency rate of 96.0% in 1997, 98.0% in 1998 and 99.1% in 1999, respectively, in 618 MIDCAB patients. The conversion rate to sternotomy was 3.4% [32]. The major advantages of MIDCAB surgery are avoidance of cardiopulmonary bypass and avoidance of a complete sternotomy [4]. Avoidance of sternotomy decreases risk of infection and shortens hospital stay compared to conventional CABG [17]. Despite these advantages MIDCAB is technically demanding and still more invasive than PCI. It entails a longer mean hospital stay as compared to PCI (on average 7 days vs 3 days in this analysis). In this study, when compared to PCI using bare metal stents, the need for additional revascularization procedures was statistically better for patients having MIDCAB surgery. This difference was absent if the trial using DES stent was included in the meta-analysis.

One of the major limitations of the present study when extrapolating it to present day is the low rate of use of drug eluting stents and absence of use of glycoprotein 2b/3a inhibitors. The number of events in the meta-analysis (particularly death and myocardial infarction) were too small to draw definite conclusions. The significant difference between PCI and MIDCAP for the composite end point of mortality, myocardial infarction and target vessel revascularization was driven by the increased number of revascularizations in the PCI group. It is evident from recent trials that DES stents have a significantly lower risk of short-term in-stent stenosis than bare metal stents. The relative risk was significant at 2.27 after the trial using DES was excluded from the analysis; also the study heterogeneity decreased from 66 to 19% when the study using DES was removed from our analysis. The change in the results reflects the lower rate of restenosis with DES and possibly longer administration of the required antiplatelet therapy. Recent studies have shown rate of late stent thrombosis in DES to be similar to that for bare metal stents, so DES stent implantation appears to be an attractive option [33].

In none of the included trials could the role of volume of interventions per operator and institution be examined, even though this may significantly impact the outcome after both MIDCAB and PCI. Follow-up was significantly different and short between the trials (this impacts on the need for repeat intervention which is one of the endpoints assessed). No information was provided on the administration of statins, angiotensin-converting enzyme inhibitors or b-blockers to the two groups. All trials did not report on the frequency of anginal symptoms after revascularization. Finally, subjects at high risk for perioperative mortality, in particular, those with left ventricular dysfunction, were excluded from all trials.

No economic or cost-effective analysis was performed in this study, and thus no quantitative conclusion can be drawn on the economic comparison of MIDCAB versus PCI in a resource conscious health care setting. To further improve our understanding of the effectiveness of MIDCAB versus PCI for isolated proximal LAD lesion new larger randomized trials are needed. These trials need to be sufficiently large and properly designed and conducted and cover long-term follow-up and be reported according to the CONSORT statement [34]. The trials included in this meta-analysis do not strictly comply with CONSORT guidelines because if very strict CONSORT selection criteria are used, there are very few trials to analyze, however all trials included mention >70% of the items noted in the CONSORT checklist.
The results of this meta-analysis provide an updated and thorough comparison of MIDCAB versus PCI in management of proximal LAD stenosis. Both PCI and MIDCAB techniques have improved over time, and DES use is standard currently in patients undergoing PCI of the proximal LAD. Therefore, the results of this analysis may not be quite applicable to contemporary practice. However, the results provide a solid basis for a future randomized trial in this area.

In conclusion, the present meta-analysis of randomized trials of MIDCAB versus PCI shows that overall mortality and myocardial infarction rates are similar in stenting versus MIDCAB but surgery is still associated with significantly lower rates of revascularization in comparison to bare metal stenting. The number of randomized patients and events were small. The effect of drug eluting stents needs to be determined in future large randomized trials with long-term follow-up comparing PCI versus MIDCAB for this lesion.

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