Mortality and myocardial infarction following surgical versus percutaneous revascularization of isolated left anterior descending artery disease: a meta-analysis

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Received 21 June 2005; received in revised form 25 July 2005; accepted 27 July 2005; Available online 7 December 2005

Abstract

Objective: Despite numerous studies comparing surgical versus percutaneous revascularization, the optimal treatment of patients with isolated left anterior descending (LAD) artery disease remains debated. We conducted a meta-analysis to study the early and mid-term outcomes following percutaneous and surgical treatment of isolated LAD disease.

Methods: Medline, EMBASE, and the Cochrane databases were searched and a hand search of bibliographies was conducted. Clinical data was extracted independently by two individuals. Random effects models were used to calculate pooled risk ratios (RR) and meta-regression was employed to explain study heterogeneity. Stratified analyses were conducted and a funnel plot was used to assess publication bias.

Results: Eight randomized trials (1110 patients; median follow-up: 2.1 years, range: 0.5—5 years) and nine observational studies (12,209 patients; median follow-up: 3 years, range: 0.5—5.5 years) were identified and analyzed separately. Both randomized and observational studies demonstrated a beneficial effect of surgery compared to percutaneous therapy on mid-term major adverse cardiac events (MACE) (RR [95% CI]: 0.33 [0.24—0.46] for randomized and 0.32 [0.24—0.41] for observational studies). Studies with >1 year of follow-up demonstrated a beneficial effect of surgery compared to percutaneous therapy on combined mortality and MI rates for randomized (RR [95% CI]: 0.59 [0.35—0.98]) and observational studies (RR [95% CI]: 0.81 [0.65—0.99]). The start year was identified as a source of study heterogeneity.

Conclusions: Surgical treatment of isolated LAD disease is associated with reduced MACE, reduced mortality, and MI rates at mid-term follow-up, as well as lower recurrence of angina. Evolution of treatment strategies may explain some of the variability between studies.

Keywords: Coronary artery bypass; Minimally invasive coronary artery bypass (MIDCAB); Percutaneous transluminal coronary angioplasty; Stents; Meta-analysis; Mortality; Myocardial infarction

1. Introduction

The left anterior descending (LAD) artery supplies 50—70% of myocardial blood flow and stenosis of the proximal LAD has consistently been identified as a risk factor for cardiovascular mortality when treated with medical therapy alone [1]. Thus, the presence of a high-grade stenosis of the LAD typically warrants consideration of a revascularization procedure. Surgical and percutaneous methods of coronary revascularization have evolved significantly over recent years; surgical revascularization using the left internal mammary artery offers the advantage of durability with patency rates over 90% at 10 years [2], but is invasive and associated with an increased hospital stay. Advances in surgical techniques have led to a reduction in these early costs of surgery through the adaptation of a minimally invasive approach to LAD bypass (MIDCAB) [3].

Percutaneous therapy is relatively non-invasive, and with the use of routine stenting, carries a low incidence of early complications. However, percutaneous interventions have a significant rate of treatment failure, due to re-stenosis, with patients requiring repeat interventions. The recent introduction of drug eluting stents has led to significant reduction in the re-stenosis rates observed with stenting [4]. Since January 2002, there have been five randomized trials published comparing percutaneous and surgical treatments for isolated LAD disease [5—9]. This activity reflects the intensity of the ongoing debate between cardiologists and cardiac surgeons with respect to isolated LAD treatment. Major limitations of randomized trials in this area include...
small sample sizes, rapidly evolving techniques and technologies, and carefully selected patients, which limits generalizability. All of the randomized studies were powered to detect a difference in major adverse cardiac events (MACE) which is a composite endpoint including all-cause mortality, myocardial infarction (MI), and target vessel revascularization (TVR). Since TVR is the most frequently occurring event and reflects the major difference between surgical and percutaneous therapy, randomized trials powered to detect differences in MACE inevitably fail to detect any differences in the more clinically significant endpoints of mortality and MI due to a lack of power. Similarly, observational studies suffer from residual confounding, incomplete or biased ascertainment of certain endpoints, and selection bias which makes their results unreliable. The aim of this meta-analysis was to determine the effect of surgical versus percutaneous treatment of isolated LAD disease on early (less than 30 days) and mid-term (1 month to 5 years) outcomes with a particular focus on the more clinically relevant endpoints of mortality and myocardial infarction.

2. Materials and methods

The analyses and reporting were conducted according to the published guidelines in the QUORUM and MOOSE statements [10,11].

2.1. Data sources and study selection

We searched MEDLINE, EMBASE, the Cochrane Controlled Trials Register, and Cochrane Database of Systematic Reviews, from their inception to February 2005. Search terms included left anterior descending artery, left internal thoracic/mammary artery, angioplasty, stent, percutaneous coronary intervention, coronary artery bypass, MIDCAB, OPCAB. The bibliographies of selected articles were examined to ensure that all relevant publications had been identified. Unpublished studies were not included. The flowchart for study selection is depicted in Fig. 1. Of the 651 reports identified, 618 were excluded after reviewing the title and/or abstract. Excluded reports included case reports, reviews, editorials, and comments, studies including multivessel disease, and studies lacking either a surgical or percutaneous treatment arm. Forty-nine publications were obtained for complete review, of which 32 were excluded because they included duplicate publications, multivessel disease, and one non-English article that could not be obtained. Endpoints of interest were MACE (composite of mortality, MI, and TVR) and the combination of mortality and MI and studies were included if they reported at least one of the endpoints of interest. The final data set included eight randomized studies and nine observational studies with one observational study providing a comparison of angioplasty versus stenting versus surgery and therefore allowing two separate comparisons.

2.2. Data extraction

Two investigators independently extracted the data, using a standardized form, and all discrepancies were resolved by consensus. In addition to the above-mentioned endpoints, the following information was extracted from all studies: lead author, year of publication, start year of study, type of surgical, and percutaneous treatment, single versus multicenter study, duration of follow-up, location and severity of LAD disease, angiographic follow-up, rates of angina recurrence, costs of treatment, and quality of life (QOL) assessments when available. Adjusted rates of various outcomes were used, whenever available, from observational studies. The main endpoints of MACE, mortality, and MI were most often extracted from a summary table. For the composite MACE endpoint, each patient contributed only once to the composite endpoint. In cases where one patient reached more than one endpoint, only the first endpoint reached was counted in order to avoid double counting. The combined rates of mortality and MI were obtained by adding the individual rates in each study.

2.3. Statistical analysis

Natural logs of risk ratios (RR) were used as the primary effect estimate. Although tests for homogeneity were not
statistically significant, a number of sources of heterogeneity were anticipated a priori including study design, study start date, types of surgical and percutaneous therapies employed, and duration of follow-up. Therefore, DerSimonian and Laird random effects models were used to calculate the summary effect estimates and 95% confidence intervals. Sources of heterogeneity were examined using meta-regression techniques. Stratified analyses were performed to evaluate the effect of study type, duration of follow-up, and start year of study. Publication bias was assessed using a Begg’s Funnel plot. All statistical analyses were performed using STATA version 8 (STATA corporation, College Station, TX, USA).

3. Results

The eight randomized controlled trials included data from 1,110 patients with a median follow-up of 2.1 years (range: 0.5–5.0 years) and the nine observational studies included 12,209 patients with a median follow-up of 3.0 years (range: 0.5–5.5 years). All randomized studies reported MACE endpoints along with their individual components, whereas one observational study only reported survival data and two reported MACE endpoints without the individual components. Characteristics of randomized and observational studies are presented in Table 1.

3.1. Randomized studies

The pooled RR for randomized studies for early MACE was 0.81 (95% CI: 0.48, 1.37) indicating that a statistically significant difference was not observed between the two groups. The mid-term MACE outcomes demonstrated a beneficial effect of surgery with a RR of 0.33 (95% CI: 0.24, 0.46). The combined risk of mid-term mortality and MI was 35% lower for the surgically treated group (pooled RR [95% CI]: 0.65 [0.41, 1.02]) when all randomized studies were included and reached statistical significance when only studies with greater than 1 year follow-up were included (pooled RR [95% CI]: 0.59 [0.35, 0.98]). Surgical treatment was also associated with reduced rates of angina recurrence (pooled RR [95% CI]: 0.56 [0.38, 0.83]). The tests for study heterogeneity were non-significant for all of the above analyses (Fig. 2).

3.2. Observational studies

Unlike randomized studies, the analysis of observational studies demonstrated a protective effect of surgery on early MACE with a pooled RR of 0.32 (95% CI: 0.16, 0.63). The benefit of surgery on mid-term MACE outcomes was also evident in this group (pooled RR [95% CI]: 0.59 [0.35, 0.98]). Surgical treatment was also associated with reduced rates of angina recurrence (pooled RR [95% CI]: 0.56 [0.38, 0.83]). The tests for study heterogeneity were non-significant for all of the above analyses (Fig. 2).

3.3. Analysis of study heterogeneity

Analyses were conducted to identify potential sources of study heterogeneity as well as to account for the discrepant results between the randomized and observational studies with respect to early outcomes. The stratified analyses, using mid-term MACE as the outcome, were conducted with respect to study type, start year of the study, and duration of follow-up and are shown in Fig. 4. Studies conducted retrospectively, started prior to 1993, and with a follow-up greater than 2 years demonstrated a larger protective effect of surgery on mid-term outcome.

In order to explain the significant heterogeneity observed in the early MACE endpoint, meta-regression techniques
were employed. Although study type, start year of study, type of surgical treatment, and type of percutaneous treatment were all significant univariate predictors, the multivariate model identified only the start year of the study as a significant predictor ($p = 0.04$). This implies that the within-study heterogeneity can be explained, in part, by the study start time with older studies favoring surgical treatment more than newer ones. A Funnel plot constructed using mid-term outcomes did not demonstrate significant publication bias (Egger's test $P = 0.26$).

4. Discussion

In this meta-analysis, we have demonstrated that in addition to reduced mid-term major adverse cardiac events, surgical treatment is associated with a significant reduction of 19—35% in combined mortality and MI rates at a median follow-up of 2—3 years, an observation supported by both randomized and observational studies. Although, this difference in the combined mortality and MI rates is suggested by some of the trials, it did not reach statistical significance in the majority of the individual studies, probably due to the small number of patients studied in each trial. We also observed a benefit of surgery with respect to early MACE in the observational studies, which was not seen in the randomized trials. We also identified the start year of the study as a major source of variation among studies using a meta-regression approach.

With the rapid evolution of both surgical and percutaneous revascularization techniques and technologies, the optimal treatment of isolated LAD disease remains extensively debated. The durability and the invasiveness of the surgical approach have to be balanced with the relatively less invasive percutaneous treatment, which is associated with the need for repeat revascularization procedures. Ultimately, the goal of any revascularization procedure is to relieve angina, prevent further myocardial damage, and reduce cardiovascular mortality.

The limitations of observational studies with respect to residual and unmeasured confounding, selection bias, and inaccurate or incomplete ascertainment of clinical outcomes are well known. Randomized clinical trials in this area also face a number of unique challenges. First, cardiologists and cardiac surgeons need to agree on the patient population in whom clinical equipoise exists with respect to treatment strategy. Second, technical criteria defining the types of lesions that can be treated satisfactorily by both strategies have to be agreed upon. And finally, the prospect of randomizing patients to a surgical versus non-surgical treatment often negatively impacts recruitment. Not surprisingly, the published randomized trials are often small, underpowered to detect differences in the uncommon but more clinically relevant endpoints, and consist of a carefully selected, usually healthier, patient population compared to observational studies [9]. Furthermore, due to the slow recruitment, the need for long-term follow-up, and the...
associated with a reduction in MACE as well as the combined randomized studies suggests that surgical treatment is superior to percutaneous therapy. Future studies evaluating newer technologies like drug-eluting stents and video and robotic-assisted surgery should continue to study this question, with a particular focus on clinically significant endpoints of mortality and MI in order to provide greater insight into the optimal treatment of patients with isolated left anterior descending artery disease.

5. Limitations

A limitation of this meta-analysis is that the pooled estimates are driven by data from older studies employing treatment techniques which are now considered obsolete. However, the longer term follow-up required to detect differences in the relatively uncommon endpoints of mortality and MI can only be obtained from studies which were conducted a number of years ago. The stratified analysis suggests that longer duration of follow-up and older start year of the study similarly affect the relative benefit of surgery over percutaneous therapy implying that both are important variables affecting the pooled effect estimates. Therefore, the benefit of surgery seen in this analysis could be due to the older percutaneous treatment techniques which are now significantly improved, but may also be because the advantage of surgery is realized only at mid-term follow-up. Even though this meta-analysis was restricted to published studies, the funnel plot did not indicate significant publication bias, which provides some support for the search and study selection strategies employed.

6. Conclusions

In conclusion, pooled analysis of observational and randomized studies suggests that surgical treatment is associated with a reduction in MACE as well as the combined rate of mortality and MI at mid-term follow-up compared to percutaneous therapy. Future studies evaluating newer technologies like drug-eluting stents and video and robotic-assisted surgery should continue to study this question, with a particular focus on clinically significant endpoints of mortality and MI in order to provide greater insight into the optimal treatment of patients with isolated left anterior descending artery disease.

Acknowledgements

The authors would like to acknowledge Emily Levitan and Dr Simin Liu for their assistance with the analysis, and Dr Stuart Pocock for reviewing the manuscript. Dr Boohdwan is supported by a grant from the National Institutes of Health (HL04095-06) and the Irving Bard Memorial Fellowship.

References


Appendix A. Conference discussion

Dr. L. Von Segesser (Lausanne, Switzerland): The paper is open for discussion, anybody who wants to defend percutaneous procedures.

Dr. M. Sousa Uva (Lisbon, Portugal): I don’t want to defend percutaneous intervention, but I think this study should be published in a cardiology journal, first of all, even though they won’t make it easy to publish.

More seriously, as you said, the problem is either you have long-term follow-up or you have the up-to-date treatment. You can never have both. So even if you had stents, they were not drug-eluting stents. So the controversy will continue forever, but I think, nevertheless, it is important to study and have studies like the one you just presented now.

Dr. Boodhwani: I agree that this is an ongoing evaluation. One of the issues is that current randomized studies have relatively small sample sizes. The largest of these studies had a sample size of approximately 200 patients. So it is important every so often to perform a meta-analysis which allows us to synthesize all of the collected data to-date and evaluate outcomes in that manner.

Dr. R. Stanbridge (London, UK): I agree. I think it’s very valuable. The problem is that one of your conclusions is that pre-1993 studies are valuable. The problem is that the cardiologists know and they’re already talking about 2004 studies. Now, I think you have a very nice analysis there, but it’s kind of going to miss the point with a quarter of the people not having stents at all, which is a problem. I congratulate you on the enormous amount of hard work you’ve done to get the various studies, but I don’t know how we can persuade the cardiologists to change their practice.

Dr. Von Segesser: We can’t because there are more of those.

Dr. Boodhwani: I acknowledge that as a limitation of this meta-analysis, but that is the literature that’s currently published and these are the conclusions that we can draw from it.