



ELSEVIER

European Journal of Cardio-thoracic Surgery 26 (2004) 81–84

EUROPEAN JOURNAL OF  
CARDIO-THORACIC  
SURGERY

www.elsevier.com/locate/ejcts

# Meta-analysis on the effect of off-pump coronary bypass surgery<sup>☆</sup>

Geert J.M.G. van der Heijden<sup>a,b,\*</sup>, Hendrik M. Nathoe<sup>c</sup>, Erik W.L. Jansen<sup>b</sup>,  
Diederick E. Grobbee<sup>a</sup>

<sup>a</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht 3508 GA, The Netherlands

<sup>b</sup>Department Cardiothoracic Surgery, Heart Lung Centre Utrecht, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>c</sup>Department of Cardiology, Heart Lung Centre Utrecht, University Medical Center Utrecht, Utrecht, The Netherlands

Received 12 January 2004; received in revised form 16 March 2004; accepted 22 March 2004; Available online 30 April 2004

## Abstract

**Objective:** To assess the effect of conventional coronary artery bypass surgery (CABG) compared to the off-pump procedure (OPCAB). **Methods:** Based on randomised trials found in PubMed and Science Citation Index, an overall odds ratio and 95% confidence interval was calculated for the combined endpoint of mortality, stroke and myocardial infarction. **Results:** The 18 randomised trials included 1584 patients (783 OPCAB, 801 CABG). The odds ratio was 0.73 (95% CI = 0.26; 2.04) at 2-week post-surgery, 0.75 (0.39; 1.42) at 1-month post-surgery, 0.55 (0.28; 1.08) at 3-month post-surgery, and 0.66 (0.38; 1.15) at 1-year post-surgery. **Conclusions:** The outcome of this meta-analysis shows favourable results for OPCAB for the combined endpoint of mortality, stroke and myocardial infarction at short and long term follow-up. However, none of the risk reductions reach statistical significance at the conventional level. Based on our results OPCAB appears to be equivalent to CABG.

© 2004 Elsevier B.V. All rights reserved.

**Keywords:** Off-pump coronary bypass surgery; Meta-analysis; Randomised trials

## 1. Introduction

Coronary artery bypass surgery (CABG) relieves symptoms and improves prognosis in patients with coronary artery disease. It is assumed that the off-pump procedure (OPCAB) will reduce the postoperative risk of neuro-cognitive decline, mortality, stroke and myocardial infarction. Several early patient series comparing OPCAB and CABG have been published. But, the validity and precision of the results of such series of consecutive patients is limited. Randomised trials and meta-analyses provide the highest level of evidence, that is, when they are properly designed and conducted [1]. Since, the first randomised trial

comparing OPCAB and CABG was published by Vural in 1995 [2] many other appeared.

Our general aim is to assess the potential clinical benefits of OPCAB by means of a meta-analysis based on published results from randomised trials comparing OPCAB versus CABG. By pooling of these published results, we calculated an overall estimate of effect for the combined endpoint for mortality, stroke and myocardial infarction.

## 2. Methods

Relevant trials were searched in PubMed (up to August 2003), supplemented by cross-reference checking for relevant publications in the Science Citation Index. We combined various synonyms for off-pump, opcab, beating heart, octopus and cardiopulmonary bypass, with the sensitive evidence based search query for effectiveness studies of PubMed. By our search, we included all types of minimally invasive surgical techniques. We eliminated letters, meeting abstracts, editorials and animal research by using PubMed limits features. We

<sup>☆</sup> Presented at the joint 17th Annual Meeting of the European Association for Cardio-thoracic Surgery and the 11th Annual meeting of the European Society of Thoracic Surgeons, Vienna, Austria, October 12–15, 2003.

\* Corresponding author. Address: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Internal Postal address Str 6.131, P.O. Box 85500, Utrecht 3508 GA, The Netherlands. Tel.: +31-30-2509377; fax: +31-30-2505485.

E-mail address: g.vanderheijden@umcutrecht.nl (G.J.M.G. van der Heijden).

Table 1  
Results of meta-analysis for combined endpoint (mortality, stroke and myocardial infarction) for trails available up to August 2003

Time since surgery	Number of trials	References	Events/randomised		Results of meta-analysis		
			OPCAB	CABG	Pooled odds ratio	95% CI	P-value
2-Weeks	12	[2,22–27,29–33]	4/261	10/281	0.73	0.26; 2.04	0.55
1-Month	4	[8–21,34]	28/442	39/440	0.75	0.39; 1.42	0.38
3-Month	4	[8–21,33]	22/372	33/370	0.55	0.28; 1.08	0.08
1-Year	5	[8–21,27,35]	23/412	34/410	0.66	0.38; 1.15	0.15

selected full reports of randomised trials, comparing isolated OPCAB with CABG in adults diagnosed with CAD, including data on mortality, stroke and myocardial infarction.

We calculated event rates per treatment group for the combined endpoints, by dividing the number of events by the number of patients allocated. This was done according to the intention to treat principle, in which patients are analysed according to randomised allocation, irrespective of post-randomisation cross-over from OPCAB to CABG. Odds Ratio (OR) were derived from these event rates. For trials without events in one or both groups, the OR is zero and the standard error cannot be calculated. To deal with this problem, we have added the conventional 0.5 to each cell in the contingency table of these trials [3]. Data were analysed with STATA 7.0.

We explored heterogeneity of the endpoint across trials [4,5]. Subsequently, available data were pooled according to DerSimonian and Laird [6], where the log OR for every trial was weighted by the reciprocal of its variance, i.e. large studies with a smaller standard error were given more weight than smaller ones.

### 3. Results

With our search we retrieved 106 titles. Of these we excluded 36 titles concerning studies in which treatments eventually were not randomly allocated; 17 titles concerning randomised trials on OPCAB with another comparison than CABG; 16 titles for which only an abstract and no full report was available. Of the selected 37 full publications, 11 provide insufficient data to allow statistical pooling for the combined endpoint, leaving 26 titles.

Inclusion of duplicate data may ultimately affect both the magnitude and precision of the effect estimate [7]. We identified multiple reports for the OCTOPUS trial with varying endpoints and follow-up [8–12], the BHACAS-1 trial for all 200 patients or for different subgroups of patients [13–21]. By combining all available information for these trials double counting of patients or events was avoided. Thereby 18 trials remained [2,8–35], together including 1584 patients of which 783 are randomised to OPCAB, and 801 to CABG.

In their report, Wandschneider et al. [22] omit 11 patients from their analysis that crossed-over after randomisation from OPCAB to CABG. We included these in our analysis. There was no significant heterogeneity between trials with respect to outcomes. There was no genuine heterogeneity for the reported outcomes across trials [4,5] ( $P > 0.05$ ), moreover the fixed or random effects models showed similar results.

Table 1 displays the results of this meta-analysis. These results imply relative risk reductions in favour of OPCAB of 27% at 2 weeks, 25% at 1 month, 45% at 3 months and 34% at 1 year. None of these outcomes, however, reached significance at the conventional level. Fig. 1 shows the Forrest Plot for the meta-analysis at 1-year post-surgery.

### 4. Comment

The outcome of our meta-analysis shows favourable results for OPCAB for the combined endpoint of mortality, stroke and myocardial infarction at short and long term follow-up. However, none of the relatively large risk reductions reach statistical significance at the conventional level. There is too few data to warrant meta-analysis regarding the effects of OPCAB on cognitive outcomes and quality of life. And most of the available trials mainly include low risk patients for a first time coronary intervention, most frequently males at relatively low age, and few follow patients up for longer than 3 months.

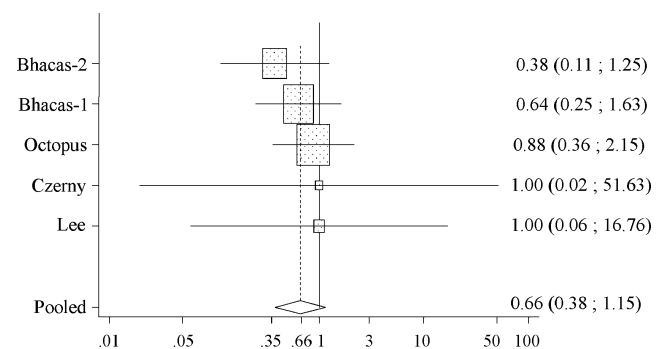


Fig. 1. Results of meta-analysis at 1-year post-surgery for combined endpoint (mortality, stroke and myocardial infarction) for trails available up to August 2003. X-axis, log scale for odds-ratio; Y-axis, odds-ratio and 95% confidence intervals for included trials. Test for heterogeneity  $Q = 1.36$  ( $df = 4$ )  $P = 0.85$ .

Based on the magnitude of the risk reductions up to 1-year post-surgery that we obtained during our pooled analysis, we conclude that OPCAB appears at least to be equivalent to CABG with respect to the combined endpoint for mortality, stroke and myocardial infarction. But, because statistical significance is not reached for the obtained risk reductions, strong clinical recommendations in favour of OPCAB cannot be given.

Clearly direct costs of OPCAB are lower, but for cost-effectiveness evaluation a long term perspective is needed, including the costs of all subsequent events and related treatment. But, currently there are too few of such data to allow firm conclusions on the cost-effectiveness of OPCAB.

We have directed our search on PubMed because it includes all relevant cardiothoracic surgery journals. Compared to previous meta-analysis our search retrieved more randomised trials, and so improves statistical power. Yet, the advantage of OPCAB compared to CABG does not reach statistical significance at the conventional level.

To further improve our understanding of the effectiveness of OPCAB new randomised trials are needed. These trials need to be sufficiently large, properly designed and conducted and cover long term follow-up and their report according to the CONSORT statement [1] (<http://www.consort-statement.org>). Apart from death, stroke, myocardial infarction, they should comprise neurocognitive outcome, quality of life, hospitalisation and re-intervention as outcomes. In addition, they should address the balance between costs and effect of OPCAB in comparison to CABG.

Currently, new randomised trials and longer term outcomes of trials that are included in this meta-analysis await full publication. Their publication will merit an update of this meta-analysis, according to the concept of cumulative meta-analysis, which was coined by Lau et al. [36]. Thereby, the statistical power will increase further, and statistical significance for superiority for OPCAB at 3-month and 1-year follow-up may be shown.

Moreover, a re-analysis of pooled raw trial data in general will result in more precise effect estimates [37], and will provide an opportunity to study the difference in effect between OPCAB and CABG more thoroughly, including the influence of pre-operative risk factors. To make such pooled re-analysis of raw trial data a success, the willingness of investigators to collaborate and share their raw trial data is essential. Currently, we invite investigators to collaborate in such research.

To date, there is no conclusive evidence on the advantage of OPCAB compared to CABG, since the relatively large observed risk reductions for the combined endpoint of death, stroke and myocardial infarction do not reach statistical significance at the conventional level. It is expected that in the near future stronger evidence will emerge from an update of this meta-analysis, either or both including new trials, or a re-analysis of pooled raw trial data.

## References

- [1] Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357:1191–4.
- [2] Vural KM, Tasdemir O, Karagoz H, Emir M, Tarcan O, Bayazit K. Comparison of the early results of coronary artery bypass grafting with and without extracorporeal circulation. *Thorac Cardiovasc Surg* 1995;43:320–5.
- [3] Yates F. Contingency tables involving small numbers and the chi-square test. *J R Stat Soc* 1934;(Suppl. 1):217–35.
- [4] Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999;18:2693–708.
- [5] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- [6] Berlin JA, Laird NM, Sacks HS, Chalmers TC. A comparison of statistical methods for combining event rates from clinical trials. *Stat Med* 1989;8:141–51.
- [7] Tramer MR, Reynolds DJ, Moore RA, McQuay HJ. Impact of covert duplicate publication on meta-analysis: a case study. *Br Med J* 1997;315:635–40.
- [8] van Dijk D, Nierich AP, Eefting FD, Buskens E, Nathoe HM, Jansen EW, Borst C, Knape JT, Bredee JJ, Robles De Medina EO, Grobbee DE, Diephuis JC, de Jaegere PP. The Octopus Study: rationale and design of two randomized trials on medical effectiveness, safety, and cost-effectiveness of bypass surgery on the beating heart. *Control Clin Trials* 2000;21:595–609.
- [9] vanDijk D, Keizer AM, Diephuis JC, Durand C, Vos LJ, Hijman R. Neurocognitive dysfunction after coronary artery bypass surgery: a systematic review. *J Thorac Cardiovasc Surg* 2000;120:632–9.
- [10] van Dijk D, Nierich AP, Jansen EW, Nathoe HM, Suyker WJ, Diephuis JC, van Boven WJ, Borst C, Buskens E, Grobbee DE, Robles De Medina EO, de Jaegere PP. Early outcome after off-pump versus on-pump coronary bypass surgery: results from a randomized study. *Circulation* 2001;104:1761–6.
- [11] van Dijk D, Jansen EW, Hijman R, Nierich AP, Diephuis JC, Moons KG, Lahpor JR, Borst C, Keizer AM, Nathoe HM, Grobbee DE, de Jaegere PP, Kalkman CJ. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. *J Am Med Assoc* 2002;287:1405–12.
- [12] Nathoe HM, van Dijk D, Jansen EW, Suyker WJ, Diephuis JC, van Boven WJ, delaRiviere AB, Borst C, Kalkman CJ, Grobbee DE, Buskens E, de Jaegere PP. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. *N Engl J Med* 2003;348:394–402.
- [13] Lloyd CT, Ascione R, Underwood MJ, Gardner F, Black A, Angelini GD. Serum S-100 protein release and neuropsychologic outcome during coronary revascularization on the beating heart: a prospective randomized study. *J Thorac Cardiovasc Surg* 2000;119:148–54.
- [14] Ascione R, Williams S, Lloyd CT, Sundaramoorthi T, Pitsis AA, Angelini GD. Reduced postoperative blood loss and transfusion requirement after beating-heart coronary operations: a prospective randomized study. *J Thorac Cardiovasc Surg* 2001;121:689–96.
- [15] Ascione R, Caputo M, Calori G, Lloyd CT, Underwood MJ, Angelini GD. Predictors of atrial fibrillation after conventional and beating heart coronary surgery: A prospective, randomized study. *Circulation* 2000;102:1530–5.
- [16] Ascione R, Lloyd CT, Underwood MJ, Gomes WJ, Angelini GD. On-pump versus off-pump coronary revascularization: evaluation of renal function. *Ann Thorac Surg* 1999;68:493–8.
- [17] Ascione R, Lloyd CT, Underwood MJ, Lotto AA, Pitsis AA, Angelini GD. Inflammatory response after coronary revascularization with or without cardiopulmonary bypass. *Ann Thorac Surg* 2000;69:1198–204.
- [18] Cox CM, Ascione R, Cohen AM, Davies IM, Ryder IG, Angelini GD. Effect of cardiopulmonary bypass on pulmonary gas

- exchange: a prospective randomized study. *Ann Thorac Surg* 2000; 69:140–5.
- [19] Ascione R, Lloyd CT, Underwood MJ, Lotto AA, Pitsis AA, Angelini GD. Economic outcome of off-pump coronary artery bypass surgery: a prospective randomized study. *Ann Thorac Surg* 1999;68:2237–42.
- [20] Angelini GD, Taylor FC, Reeves BC, Ascione R. Early and midterm outcome after off-pump and on-pump surgery in Beating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2): a pooled analysis of two randomised controlled trials. *Lancet* 2002;359:1194–9.
- [21] Ascione R, Lloyd CT, Gomes WJ, Caputo M, Bryan AJ, Angelini GD. Beating versus arrested heart revascularization: evaluation of myocardial function in a prospective randomized study. *Eur J Cardiothorac Surg* 1999;15:685–90.
- [22] Wandschneider W, Thalmann M, Trampitsch E, Ziervogel G, Kobinia G. Off-pump coronary bypass operations significantly reduce S100 release: an indicator for less cerebral damage? *Ann Thorac Surg* 2000; 70:1577–9.
- [23] Gulielmos V, Eller M, Thiele S, Dill HM, Jost T, Tugtekin SM, Schueler S. Influence of median sternotomy on the psychosomatic outcome in coronary artery single-vessel bypass grafting. *Eur J Cardiothorac Surg* 1999;16(Suppl 2):S34–8.
- [24] Gulielmos V, Menschikowski M, Dill H, Eller M, Thiele S, Tugtekin SM, Jaross W, Schueler S. Interleukin-1, interleukin-6 and myocardial enzyme response after coronary artery bypass grafting—a prospective randomized comparison of the conventional and three minimally invasive surgical techniques. *Eur J Cardiothorac Surg* 2000;18: 594–601.
- [25] Diegeler A, Hirsch R, Schneider F, Schilling LO, Falk V, Rauch T, Mohr FW. Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. *Ann Thorac Surg* 2000;69:1162–6.
- [26] Matata BM, Sosnowski AW, Galinanes M. Off-pump bypass graft operation significantly reduces oxidative stress and inflammation. *Ann Thorac Surg* 2000;69:785–91.
- [27] Czerny M, Baumer H, Kilo J, Lassnigg A, Hamwi A, Vukovich T, Wolner E, Grimm M. Inflammatory response and myocardial injury following coronary artery bypass grafting with or without cardiopulmonary bypass. *Eur J Cardiothorac Surg* 2000;17:737–42.
- [28] Czerny M, Baumer H, Kilo J, Zuckermann A, Grubhofer G, Chevtchik O, Wolner E, Grimm M. Complete revascularization in coronary artery bypass grafting with and without cardiopulmonary bypass. *Ann Thorac Surg* 2001;71:165–9.
- [29] Baker RA, Andrew MJ, Ross IK, Knight JL. The Octopus II stabilizing system: biochemical and neuropsychological outcomes in coronary artery bypass surgery. *Heart Surg Forum* 2001;4(Suppl 1): S19–S23.
- [30] Penttila HJ, Lepojarvi MV, Kiviluoma KT, Kaukoranta PK, Hassinen IE, Peuhkurinen KJ. Myocardial preservation during coronary surgery with and without cardiopulmonary bypass. *Ann Thorac Surg* 2001;71: 565–71.
- [31] Tang AT, Knott J, Nanson J, Hsu J, Haw MP, Ohri SK. A prospective randomized study to evaluate the renoprotective action of beating heart coronary surgery in low risk patients. *Eur J Cardiothorac Surg* 2002;22:118–23.
- [32] Velissaris T, Tang A, Murray M, El Minshawy A, Hett D, Ohri S. A prospective randomized study to evaluate splanchnic hypoxia during beating-heart and conventional coronary revascularization. *Eur J Cardiothorac Surg* 2003;23:917–24.
- [33] Zamvar V, Williams D, Hall J, Payne N, Cann C, Young K, Karthikeyan S, Dunne J. Assessment of neurocognitive impairment after off-pump and on-pump techniques for coronary artery bypass graft surgery: prospective randomised controlled trial. *Br Med J* 2002; 325:1268.
- [34] Puskas JD, Williams WH, Duke PG, Staples JR, Glas KE, Marshall JJ, Leimbach M, Huber P, Garas S, Sammons BH, McCall SA, Petersen RJ, Bailey DE, Chu H, Mahoney EM, Weintraub WS, Guyton RA. Off-pump coronary artery bypass grafting provides complete

revascularization with reduced myocardial injury, transfusion requirements, and length of stay: a prospective randomized comparison of two hundred unselected patients undergoing off-pump versus conventional coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003;125:797–808.

- [35] Lee JD, Lee SJ, Tsushima WT, Yamauchi H, Lau WT, Popper J, Stein A, Johnson D, Lee D, Petrovitch H, Dang CR. Benefits of off-pump bypass on neurologic and clinical morbidity: a prospective randomized trial. *Ann Thorac Surg* 2003;76:18–25.
- [36] Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med* 1992;327:248–54.
- [37] Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993;341: 418–22.

## Appendix A. Conference discussion

**Mr V. Zamvar (Edinburgh, UK):** Two of the common criticisms leveled against the technique of off-pump surgery is that, one, the quality of the anastomosis suffers because it is perceived to be technically more demanding, and second, there are less numbers of grafts and this results in incomplete revascularization, and these are all based on case studies and observational studies. Based on your meta-analysis of randomised controlled trials, do you have any data about angiographic patency in these two groups and also about the number of grafts that these patients had? So what I am asking you is, based on your meta-analysis of randomised controlled trials, can you refute these criticisms?

**Dr Jansen:** I think we can say that the first series of randomised trials really present the routine group of patients, and these are not the groups of patients with very much diffuse coronary artery disease, so these are patients which are good for a study, and the majority of patients didn't have three, four, five grafts. It is the early stage of this study in most centers, and we have to wait for the next trials that will include also the most extensive revascularizations, like five grafts in one patient and evaluation of patency.

**Dr C. Alhan (Istanbul, Turkey):** We all know that patients who have converted to on-pump surgery have higher morbidity and mortality rates, and in many of these studies, these patients were excluded from the study. I know that you are a member of the OPCAB study group, and in that study 7.7% of the patients were converted to on-pump surgery and were excluded from the study. Would you please comment on that?

**Dr Jansen:** The conversion rate in this series is very, very low. The randomised trials came from centers who have a large experience in beating heart surgery, and the conversion rate actually is below 1%, and that is rare. And I think that it is typically also a matter of experience; in initial experience, in early experience, surgeons can have sudden conversions for technical reasons, but for emergency conversions the rate is so low.

But it is a learning curve; we have to train younger surgeons also how to do off-pump surgery. But if you really are experienced with it, the conversion rate is, well, not really an issue, but you must have to have your pumps somewhere standby for a technical reason, of course.

**Dr O. Penn (Eindhoven, The Netherlands):** There is something that I fail to understand. How come that in your slides you tell us that there is a small, nonsignificant effect in favor of OPCAB but in your abstract you are talking about a marked statistically significant effect in favor of OPCAB?

**Dr Jansen:** This is actually the result of hard work in the last week, because then the SMART study became available and a few others also. Therefore, we had to adapt our presentation. Really last month's randomised trials were included, and therefore the significance was lower than in the abstract. So I showed you one Note slide, "Please see that data are adjusted."

And you could also see on one of my slides that most studies are very, very small and the studies really say a lot about the current status of randomised studies, that, the biggest studies have appeared very recently. So that was the reason why we had to adjust our conclusion.