On- vs. off-pump coronary artery bypass grafting: A systematic review and meta-analysis

Dieberg, Gudrun; Smart, Neil A.; King, Nicola

Published in:
International Journal of Cardiology

DOI:
10.1016/j.ijcard.2016.08.250

Publication date:
2016

Document version:
Peer reviewed version

On- vs. off-pump coronary artery bypass grafting: a systematic review and meta-analysis

Gudrun Dieberg PhD[1], Neil A. Smart PhD[1] & Nicola King PhD[2]

1. School of Science and Technology, University of New England, Armidale, NSW 2350, Australia. These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

2. School of Biomedical and Healthcare Sciences, Plymouth University Peninsula Schools of Medicine and Dentistry, University of Plymouth, Plymouth, PL4 8AA, UK. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Address for Correspondence:School of Biomedical and Healthcare Sciences

Plymouth University Peninsula School of Medicine and Dentistry

University of Plymouth

Plymouth, PL4 8AA, UK.

Tel: +44 1752 584969

e-mail: nicola.king@plymouth.ac.uk

Funding source: none

Conflicts of interest: none declared

Key words: coronary artery bypass graft; stroke; off-pump; on-pump; hospital costs

Running head: On- vs. Off-pump during CABG

Word Count – Full text: 5,080 words

ABSTRACT

Background: To reduce complications during coronary artery bypass grafting (CABG) off-pump CABG was introduced; however, results have been mixed. The aim of this work was to conduct a systematic review and meta-analysis of off-pump vs. on-pump CABG.

Methods: To identify potential studies systematic searches were carried out using various databases. The search strategy included the key concepts of "cardiopulmonary bypass" AND "coronary artery bypass grafting" AND "off pump". This was followed by a meta-analysis investigating post-operative atrial fibrillation, myocardial infarction, ≤30 day mortality, stroke, ventilation time, intensive care unit (ICU) stay and hospital stay.

Results: Fifty four studies (59 intervention groups), totalling 16,261 participants were analysed. Off pump CABG led to a significantly lower incidence of post-operative atrial fibrillation Odds ratio (OR) 0.87 (95% confidence interval [CI] 0.78 to 0.97, p=0.01), but no differences in either myocardial infarction OR 0.98 (95% CI 0.82 to 1.15, p=0.77) or ≤30 day mortality OR 0.85 (95% CI 0.68 to 1.06, p=0.16). There was a strong trend toward a reduced incidence of stroke OR 0.77 (95% CI 0.59 to 1.00, p=0.05); however this did not quite reach significance. Ventilation time mean difference (MD) -3.78 hours (95% CI -4.75 to -2.82, p<0.00001); ICU stay MD -0.34 days (95% CI -0.50 to -0.17, p<0.0001); and hospital stay MD -0.9 days (95% CI -1.25 to -0.56, p<0.00001) were all significantly shorter in the off-pump group.

Conclusions: Off-pump CABG has some benefits over on-pump CABG, particularly in relation to post-operative atrial fibrillation.

Word Count: 248

KEYWORDS: coronary artery bypass graft; hospital costs; off-pump; on-pump

INTRODUCTION

The usual approach to surgical revascularisation is coronary artery bypass grafting (CABG) involving cardiopulmonary bypass (CPB). This procedure is not without risk as aortic manipulation and CPB increase the possibility of aortic damage, adverse neurologic events such as stroke, and renal damage [1]. At the micro level CPB is associated with pro-inflammatory responses such as the release of cytokines, increased production of reactive oxygen species and stimulation of the release of stress hormones [2]. Bleeding problems can lead to anaemia which is associated with acute myocardial infarction (MI) and higher 30-day mortality [2].

To reduce these complications off-pump CABG was introduced [1]. Originally developed in the 1960s, off-pump CABG became increasingly popular as tools were developed for immobilising the myocardium (for examples see Figure 1 in [1]). However, enthusiasm over this approach has been tempered by difficulties in accessing lateral or posterior wall vessels [1] and the surgeon's expertise and experience. In a large multi-centre study (CORONARY) off-pump CABG was associated with lower rates of postoperative blood transfusion and reoperation for bleeding but no differences in MI, stroke and new-onset renal failure at either 30 days or 1-year [3-4]. This pattern of reduced bleeding complications and new onset atrial fibrillation but no effect on MI and stroke has been repeated in other trials [5]. Because of its failure to reduce the incidence of stroke and the possible need for repeat revascularisation, off-pump CABG is not without its detractors (for example [6]).

There has been a number of meta-analyses comparing on-pump vs. off-pump, such as those by Afilalo et al [5] and Kuss et al [7] and the 2012 Cochrane review [8]. New studies are emerging all the time and these meta-analyses have been superseded by more recent studies [9, 10]. The current meta-analysis includes more studies (and intervention groups) than that by Deppe et al [9] and also considers resource allocation (ventilation time, ICU stay, hospital stay) which was not analysed by Kowalewski et al [10]. In total our analyses included incidence of post-operative atrial fibrillation, incidence of myocardial infarction, mortality, incidence of stroke, ventilation time, ICU stay and hospital stay.

METHODS

Search strategy

To identify potential studies systematic searches were carried out using the following databases: EMBASE, PubMed, Web of Science and the Cochrane Central Registry of Controlled Trials (CENTRAL). The search was supplemented by scanning the reference lists of eligible studies. The search strategy included the key concepts of "cardiopulmonary bypass" AND "coronary artery bypass grafting" AND "off pump". All identified papers were assessed independently by two reviewers. A third reviewer was consulted to resolve disputes. Searches of published papers were conducted up until January 1st, 2016.

Types of studies to be included

Only randomized controlled trials (RCTs) and their substudies where this did not involve duplication of data of off-pump vs. on-pump in patients undergoing CABG were included. There were no language restrictions. Animal studies, review papers and non-randomized controlled trials were excluded. Studies that did not have any of the desired outcome measures or participants who were treated by other modalities such as percutaneous coronary intervention were excluded. Incomplete data, or data from an already included study, were excluded. Studies that included interventions other than off-pump vs. on-pump CABG were excluded.

Participants/population

This meta-analysis analysed RCTs and their substudies where this did not involve duplication of data of both male and female adult (≥18 years) patients with coronary artery disease who were undergoing CABG using either off- or on-pump. Other treatment modalities and interventions for coronary artery disease such percutaneous coronary intervention were excluded.

Intervention(s), exposure(s)

This meta-analysis considered all RCTs and their substudies where this did not involve duplication of data where patients with stable angina or acute coronary syndrome being treated with CABG were exposed to either on-pump or off-pump. More specifically, all RCTs and their substudies where this did not involve duplication of data where the intervention of carrying out CABG without the use of cardiopulmonary bypass were performed.

Comparator(s)/control

The studies in this analysis compared off-pump CABG with a usual care control group receiving on-pump CABG.

Search Results

Our initial search found 2,161 articles. Of these 2,055 studies were excluded on the basis of title and abstract. 36 studies were excluded as they were not RCTs. Of the RCTs we excluded 16 studies, because they had none of the reported measures (see supplementary Figure S1). Fifty five studies were included in our analysis [3, 11-63].

Outcome(s)

The primary outcomes analysed were: incidence of post-operative atrial fibrillation, incidence of myocardial infarction, ≤30 day mortality, incidence of stroke, ventilation time, ICU stay and length of hospital stay.

Risk of bias (quality) assessment

Risk of bias was assessed using a modification of the JADAD scale [64].

Strategy for data synthesis

Odds ratios were calculated for dichotomous data. An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. Mean differences were calculated for continuous data. Meta-analyses were completed for continuous data by calculating the mean difference between intervention and control groups from post-intervention data only. It is an accepted practice to only use post-intervention data for meta-analysis, but this method assumes that random allocation of participants always creates intervention groups matched at baseline for age, disease severity. All analyses were conducted using Revman 5.0 (Nordic Cochrane Centre, Denmark). A fixed effects inverse variance model was used unless heterogeneity was >75%, then a random effects model was used. Heterogeneity was quantified using the Cochrane Q test [65]. We used a 5% level of significance and 95% confidence intervals; figures were produced using Revman 5.3.

RESULTS

The 54 studies (59 intervention groups) included in the analyses had an aggregate of 16,255 participants, 8,156 of which had on-pump CABG and 8,099 had off-pump CABG. Table 1 summarizes the characteristics of the included studies. Supplementary Table S1 lists the excluded RCTs and reasons for exclusion.

Post-operative Atrial Fibrillation

Nineteen studies (22 intervention groups) reported post-operative atrial fibrillation. The odds ratio (OR) for the pooled analysis was 0.87 (95% Confidence Interval (CI) 0.78 to 0.97, p=0.01), see Figure 1. Post-operative atrial fibrillation occurred significantly more often in the on-pump group than in the off-pump group. Overall, the incidence of post-operative atrial fibrillation was 19.4% in the off-pump group, which was less than the 21.8% in the on-pump group.

Incidence of myocardial infarction

Thirty three studies (34 intervention groups) reported the incidence of myocardial infarction. The OR for the pooled analysis was 0.98 (95% CI 0.82 to 1.15, p=0.77) see Figure 2. Myocardial infarction was as likely to occur in the off-pump group as in the on-pump group. Overall, the incidence of myocardial infarction was 4.8% in the off-pump group, which was not significantly different to the 4.7% in the on-pump group.

≤30-day mortality

Forty one studies (43 intervention groups) reported ≤30-day mortality. The OR for the pooled analysis was 0.85 (95% CI 0.68 to 1.06, p=0.16), see Figure 3. Patients were as likely to die in the off-pump group as they were in the on-pump group. Overall, the incidence of ≤30-day mortality in the off-pump group was 1.9% which was slightly less than the 2.2% incidence in the on-pump group.

Incidence of stroke

Thirty four studies (36 intervention groups) reported the incidence of stroke. The odds ratio (OR) for the pooled analysis was 0.77 (95% CI 0.59 to 1.00, p=0.05), see Figure 4. This means that there was a strong trend towards a lower incidence of stroke in the off-pump group; however, this did not quite reach significance. Overall, the incidence of stroke in the off-pump group was 1.3% compared to 1.7% in the on-pump group.

Ventilation time

Twenty six studies (28 intervention groups) reported the ventilation time in hours. The mean difference for the pooled analysis was -3.78 hours (95% CI -4.75 to -2.82, P<0.00001), see Figure 5. Off-pump patients had significantly shorter ventilation times. The effect size was 0.77 (95% CI 0.49 to 1.06).

Intensive Care Unit (ICU) stay

23 studies (25 intervention groups) reported the duration of stay in the ICU in days. The mean difference for the pooled analysis was -0.34 days (95% CI -0.50 to -0.17, p<0.0001), see Figure 6. Off-pump patients had significantly shorter stays in the ICU. The effect size was 0.68 (95% CI 0.38 to 0.99).

Hospital stay

Twenty four studies (26 intervention groups) reported hospital stay in days. The mean difference for the pooled analysis was -0.90 days (95% CI -1.25 to -0.56, p<0.00001), see Figure 7. Off-pump CABG patients had significantly shorter hospital stays. The effect size was 0.37 (95% CI 0.22 to 0.51).

Risk of bias

Only 13 of the 54 studies had carried out allocation concealment, only 24 studies had carried out blinding and only 21 studies had performed an intention to treat analysis.

DISCUSSION

Stroke is a major cause of morbidity and mortality following cardiac surgery, especially in high risk patients. In an attempt to reduce the incidence of stroke and other post-operative complications off-pump CABG was introduced in the 1960s. However, results remain equivocal with a Cochrane review finding no differences in the incidence of mortality, stroke and myocardial infarction [8] compared with more recent meta-analyses that showed an increased incidence of stroke in the on-pump group [9, 10]. In our meta-analysis, on-pump CABG was associated with a higher incidence of post-operative atrial fibrillation, no difference in either myocardial infarction or mortality, a strong trend towards a reduced incidence of stroke in the off-pump group, and significantly shorter duration of ventilation, ICU stay and hospital stay in the off-pump group.

The incidence of post-operative atrial fibrillation was significantly lower in the off-pump group (Figure 1). Although this was the result of the pooled data analysis, it should be noted that some studies showed no difference in the incidence of post-operative atrial fibrillation [66]. Atrial fibrillation is not a life-threatening occurrence, though its presence could predispose to haemodynamic compromise, thromboembolic events, anxiety and increased costs [15]. One of the primary reasons why off-pump CABG may elicit less atrial fibrillation is that it avoids atrial cannulation.

There was no difference in the incidence of myocardial infarction (Figure 2) or ≤30 day mortality (Figure 3) between the two groups. This result is consistent with the four largest studies to date [3, 21, 28, 54] and also with recent meta-analyses [9, 10].

It is estimated that the incidence of stroke after CABG ranges from 1.1-5.7% [67]. In their systematic review on this topic Mao et al [67] identified the following as risk factors: advanced age, prior (before CABG) cerebrovascular disease/stroke, prior carotid artery stenosis, prior peripheral vascular disease, prior unstable angina, and prolonged cardiopulmonary bypass time. Post-operative atrial fibrillation was identified as an independent predictor [67]. Five of the trials involved in our meta-analysis involved patients with a mean age ≥ 70 years [see Table 1]. Off-pump CABG provided no greater protection against stroke in any of these studies (results not shown). This was also the case in the whole cohort of patients (Figure 4), although there was a strong trend towards a beneficial effect with off-pump CABG. The incidence of stroke was also not significantly different in any of the four largest trials to date [3, 21, 28, 54] and neurocognitive function was not affected in the ROOBY trial [68-69]. Our results contrast those of Deppe et al [9] possibly due to the inclusion of more studies. These conflicting findings suggest that the question as to whether off-pump CABG serves as a protector against stroke is too close to call.

In the current economic climate the cost of hospital stays is of considerable interest. In 2014-15 it was estimated that excess hospital stays cost the UK National Health Service an estimated £303 per day [70]. The cost per day for an ICU stay rises to approximately £1500 (http://www.bbc.co.uk/news/health-11503873). This might suggest that the significantly shorter ventilation time (Figure 5), ICU stay (Figure 6) and hospital stay (Figure 7) experienced by off-pump patients could reduce healthcare costs. This is supported by the results of one study [71]; however, two other reports in the literature refute this [72-73].

Study limitations: One of the limitations of the current study is the relatively small size of many of the included trials. Only three trials included >1000 patients in both the on- and off-pump groups [3, 21, 54] with many of the trials including <100 patients in both groups [e.g. 13, 17-18] and some as little as <20 per experimental group [e.g. 19, 25-26]. There were also differences in the procedure used for cardiopulmonary bypass (CPB), with some groups using normothermic CPB [e.g. 16, 19-20], whilst others used hypothermic CPB [e.g. 11, 18, 23-25] and a number of studies did not mention the type of CPB used [e.g. 26, 28-29]. In addition there were some differences in the type of cardioplegic arrest used in the on-pump groups wherein: some groups used cold blood cardioplegia [e.g. 11, 17, 19-20]; others used warm blood cardioplegia [e.g. 13-15]; some used cold crystalloid cardioplegia [e.g. 16] and others did not mention the type of cardioplegia used [e.g. 26, 29] or left this to the surgeon's discretion [e.g. 21]. The experience of the surgeons in performing off-pump procedures was rarely mentioned. Future studies on this topic should pay further attention to allocation concealment, blinding and intention to treat analysis.

Acknowledgements

We would like to thank the cardiac surgeon, Adrian Marchbank for critical reading of the manuscript.

CONFLICTS OF INTEREST

None declared

FUNDING SOURCE

None

REFERENCES

1. Neely RC, Leacche M, Byrne CR, Norman AV, Byrne JG. New approaches to cardiovascular surgery. *Curr Probl Cardiol*. 2012;39:427-466.
2. Parissis H, Mbarushimana S, Ramesh BC, Parissis M, Lampridis S. The impact of off-pump surgery in end-organ function: practical end-points. *J Cardiothorac Surg*. 2015;10:159.
3. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu SS, Paolasso E, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med*. 2012;366:1489-1497.
4. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu SS, Paolasso E, et al : Off-pump or on-pump coronary-artery bypass grafting at 1 year. *N Engl J Med*. 2013;368:1179-1188.
5. Afilalo J, Rasti M, Ohayon SM, Shimony A, Eisenberg MJ. Off-pump vs. on-pump coronary artery bypass surgery: an updated meta-analysis and meta-regression of randomized trials. *Eur Heart J*. 2012;33:1257-1267.
6. Lazar HL. Off-pump coronary artery bypass: past, present and future of a controversial technology. *Curr Opinion Cardiol*. 2015;30:629-635.
7. Kuss O, von Salviati B, Bergemann J. Off-pump versus on-pump coronary artery bypass grafting: a systematic review and meta-analysis of propensity score analyses. *J Thorac Cardiovasc Surg*. 2010;140:829-835.

8. Møller CH, Penninga L, Wetterslev J, Steinbruchel DA, Gluud C. Off-pump versus on-pump coronary artery bypass grafting for ischaemic heart disease. *Cochrane Database of Systematic Reviews*. 2012;CD007224.
9. Deppe A-Cl, Arbash W, Kuhn EW, Slottosch I, Scherner M, Liakopoulos OJ et al: Current evidence of coronary artery bypass grafting off-pump versus on-pump: a systematic review with meta-analysis of over 16900 patients investigated in randomized controlled trials. *Int J Cardiol*. 2016;49:1031-1041.
10. Kowalewski M, Pawliszak W, Malvindi PG, Bokszanski MP, Perlinski D, Raffa GM et al: Off-pump coronary artery bypass grafting improves short-term outcomes in high risk patients compared with on-pump coronary artery bypass grafting: meta-analysis. *J Thorac Cardiovasc Surg*. 2016;151:60-77.
11. Al-Ruzzeh S, George S, Bustami M, Wray J, Ilisley C, Athanasiou T et al: Effect of off-pump coronary artery bypass surgery on clinical, angiographic, neurocognitive, and quality of life outcomes: randomised controlled trial. *Br Med J.* Doi:10.1136/bmj.38852.479907.7c.
12. Almassi GH, Shroyer AL, Collins JF, Hattler B, Bishawi M, Baltz JH, et al: Chronic obstructive pulmonary disease impact upon outcomes: the veterans affairs randomized on/off bypass trial. *Ann Thorac Surg*. 2013;96:1302-1309.
13. Alwan K, Falcoz P-E, Alwan J, Mouawad W, Oujaimi G, Chocron S et al: Beating versus arrested heart coronary revascularization: evaluation by cardiac troponin I release. *Ann Thorac Surg* 2004;77:2051-2055.
14. Angelini GD, Taylor FC, Reeves BC, Acione 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;359:1194-1199.
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. *Circ.* 2000;102:1530-1535.

16. Bednar F, Osmancik P, Vanek T, Mocikova H, Jares M, Straka Z, et al: Platelet activity and aspirin efficacy after off-pump compared with on-pump coronary artery bypass surgery: results from the prospective randomized trial PRAGUE 11 – Coronary Artery Bypass and Reactivity of Thrombocytes (CABARET). *J Thorac Cardiovasc Surg* 2008;136:1054-1060.
17. Bonacchi M, Prifti E, Malani M, Bartolozzi F, Eusanio M, Leacche M. Does off-pump coronary revascularization reduce the release of the cerebral markers, S-100β and NSE? *Heart Lung and Circ.* 2006;15:314-319.
18. Chowdhury UK, Diplomate NB, Malik V, Yadav R, Seth S, Ramakrishnan L et al: Myocardial injury in coronary bypass grafting: on-pump versus off-pump comparison by measuring high-sensitivity C-reactive protein, cardiac troponin I, heart-type fatty acid-binding protein, creatine kinase-MB, and myoglobin release. *J Thorac Cardiovasc Surg.* 2008;135:1110-1119.
19. Czerny M, Baumer H, Kilo J, Lassnigg A, Hamwi A, Vukovich T et al: Inflammatory response and myocardial injury following coronary artery bypass grafting with or without cardiopulmonary bypass. *Eur J Cardio-thorac Surg.* 2000;17:737-742.
20. Czerny M, Baumer H, Kilo J, Zuckermann A, Grubhofer G, Chevtchik O et al: Complete revascularization in coronary artery bypass grafting with and without cardiopulmonary bypass. *Ann Thorac Surg.* 2001;71:165-169.
21. Diegeler A, Börgermann J, Kappert U, Breuer M, Böning A, Ursulesc A et al: Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *New Eng J Med*. 2013;368:1189-1198.
22. Dorman H, Kratz JM, Multani M, Baron R, Farrar E, Walton S et al: A prospective, randomized study of endothelin and postoperative recovery in off-pump versus conventional coronary artery bypass surgery. *J Cardiothorac Vasc Anesthesia.* 2004;18:25-29.
23. Fattouch K, Guccione F, Dioguardi P, Sampognaro R, Corrado E, Caruso M et al: Off-pump versus on-pump myocardial revascularization in patients with ST-segment

elevation myocardial infarction: a randomized trial. *J Thorac Cardiovasc Surg.* 2009;137:650-657.

24. Gerola LR, Buffolo E, Jasbik W, Botelho B, Bosco J, Brasil LA et al: Off-pump versus on-pump myocardial revascularisation in low-risk patients with one or two vessel disease: peri-operative results in a multicenter randomized controlled trial. *Ann Thorac Surg.* 2004;77:569-573.
25. Güler M, Kirali K, Toker ME, Bozbuğa N, Ömeroğlu SN, Akinci E et al: Different CABG methods in patients with chronic pulmonary disease. *Ann Thorac Surg.* 2001;71:152-157.
26. Gulielmos V, Menschikowski M, Dill H-M, Eller M, Thiele S, Tugtekin SM et al: 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 Cardio-thorac Surg.* 2000;18:594-601.
27. Hernandez F, Brown JR, Likosky DS, Clough RA, Hess AL, Roth RM et al: Neurocognitive outcomes of off-pump versus on-pump coronary artery bypass: a prospective randomized controlled trial. *Ann Thorac Surg.* 2007;84:1897-1903.
28. Houlind K, Kjeldson BJ, Madsen SN, Rasmussen BS, Holme SJ, Nielsen PH et al: On-pump versus off-pump coronary artery bypass surgery in elderly patients. Results from the Danish On-pump versus off-pump randomization study. *Circ.* 2012;125:2431-2439.
29. Iqbal J, Ghaffer A, Shahbaz A Rehman A: Stroke after coronary artery bypass surgery with and without cardiopulmonary bypass. *J Ayub Med Coll Abottabad*. 2014;26:123-128.
30. Kobayashi J, Tashiro T, Ochi M, Yaku H, Watanabe G, Satoh T et al: Early outcome of a randomized comparison of off-pump and on-pump multiple arterial coronary revascularisation. *Circ*. 2005;112:I338-I343.

31. Kochamba GS, Yun KL, Pfeffer TA, Sintek CF, Khonsari S: Pulmonary abnormalities after coronary arterial bypass grafting operation: cardiopulmonary bypass versus mechanical stabilization. *Ann Thorac Surg*. 2000;69:1466-1470.
32. Lee JD, Lee SJ, Tsushima WT, Yamauchi H, Lau WT, Popper J et al: Benefits of off-pump bypass on neurologic and clinical morbidity: a prospective randomized trial. *Ann Thorac Surg*. 2003;76:18-26.
33. Légaré J-F, Buth KJ, King S, Wood J, Sullivan JA, Friesen CH et al: Coronary bypass surgery performed off pump does not result in lower in-hospital morbidity than coronary artery bypass grafting performed on pump. *Circ.* 2004;109:887-892.
34. Lemma MG, Coscioni E, Tritto FP, Centofanti P, Fondacone C, Salica A et al: On-pump versus off-pump coronary artery bypass surgery in high risk patients: operative results of a prospective randomized trial (on-off study). *J Thorac Cardiovasc Surg*. 2012;143:625-631.
35. 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;119:148-154.
36. Matata BM, Sosnowski AW, Galiňanes M: Off-pump bypass graft operation significantly reduces oxidative stress and inflammation. *Ann Thorac Surg*. 2000;69:785-791.
37. Medved I, Anić D, Zrnić B, Oštrić M, Saftić I: Off-pump versus on-pump – intermittent aortic cross clamping – myocardial revascularisation: single center experience. *Coll Antropol*. 2008;32:381-384.
38. Michaux I, Filipovic M, Skarvan K, Bollinger D, Schumann R, Bernet F, et al: A randomized comparison of right ventricular function after on-pump versus off-pump coronary artery bypass graft surgery. *J Thorac Cardiovasc Surg*. 2011;141:361-367.

39. Modine T, Zannis C, Salleron J, Provot F, Gourlay T, Duhamel A et al: A prospective randomized study to evaluate the renal impact of surgical revascularization strategy in diabetic patients. *Interact Cardiovasc Thorac Surg*. 2010;11:406-410.
40. Møller CH, Perko MJ, Lund JT, Andersen LW, Kelbaek H, Madsen JK et al: No major differences in 30-day outcomes in high-risk patients randomized to off-pump versus on-pump coronary bypass surgery. The best bypass surgery trial. *Circ*. 2010;121:498-504.
41. Motallebzadeh R, Bland JM, Markus HS, Kaski JC, Jahangiri M: Neurocognitive function and cerebral emboli: randomized study of on-pump versus off-pump coronary artery bypass surgery. *Ann Thorac Surg*. 2007;83:475-482.
42. Muneretto C, Bisleri G, Negri A, Manfredi J, Metra M, Nodari S et al: Off-pump coronary artery bypass surgery technique for total arterial myocardial revascularization: a prospective randomized study. *Ann Thorac Surg*. 2003;76:778-783.
43. Nesher N, Frolkis I, Vardi M, Sheinberg N, Bakir I, Caselman F et al: Higher levels of serum cytokines and myocardial tissue markers during on-pump versus off-pump coronary artery bypass surgery. *J Card Surg.* 2006;21:395-402.
44. Niranjan G, Asimakopoulos G, Karagounis A, Cockerill G, Thompson M, Chandrasekaran V: Effects of cell saver autologous blood transfusion on blood loss and homologous blood transfusion requirements in patients undergoing cardiac surgery on- versus off-cardiopulmonary bypass: a randomised trial. *Eur J Cardio-Thorac Surg.* 2006;30:271-277.
45. Onorati F, Rubino AS, Nucera S, Foti D, Sica V, Santini F et al: Off-pump coronary artery bypass surgery versus standard linear or pulsatile cardiopulmonary bypass: endothelial activation and inflammatory response. *Eur J Cardio-Thorac Surg.* 2010;37:897-904.

46. Ozkara C, Guler N, Batyraliev T, Okut H, Agirbasli M: Does off-pump coronary artery bypass surgery reduce secretion of plasminogen activator inhibitor-1? *Int J Clin Pract.* 2007;61:763-767.
47. Paparella D, Galeone A, Venneri MT, Coviello M, Scrascia G, Marraudino N et al: Activation of the coagulation system during coronary artery bypass grafting: comparison between on-pump and off-pump techniques. *J Thorac Cardiovasc Surg*. 2006;131:290-297.
48. Puskas JD, Williams WH, Duke PG, Staples JR, Glas KE, Marshall JJ, et al: 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.
49. Raja SG, Haider Z, Ahmad M: Predictors of gastrointestinal complications after conventional and beating heart coronary surgery. *Surg J R Coll Surg Edinb Irel*. 2003;1:221-228.
50. Rasmussen BS, Laugesen H, Sollid J, Grønlund J, Rees SE, Toft E et al: Oxygenation and release of inflammatory mediators after off-pump compared with after on-pump coronary artery bypass surgery. *Acta Anaethesiol Scand*. 2007;51:1202-1210.
51. Rastan AJ, Bittner HB, Gummert JF, Walther T, Schewick CV, Girdauskas E et al: On-pump beating heart versus off-pump coronary artery bypass surgery – evidence of pump-induced myocardial injury. *Eur J Cardio-Thorac Surg.* 2005;27:1057-1064.
52. Sajja LR, Mannam G, Chakravarthi RM, Sompali S, Naidu SK, Somaraju B et al: Coronary artery bypass grafting with or without cardiopulmonary bypass in patients with preoperative non-dialysis dependent renal insufficiency: a randomized study. *J Thorac Cardiovasc Surg*. 2007;133:378-388.

53. Selvanayagam JB, Petersen SE, Francis JM, Robson MD, Kardos A, Neubauer S et al: Effects of off-pump versus on-pump coronary surgery on reversible and irreversible myocardial injury. A randomized trial using cardiovascular magnetic resonance imaging and biochemical markers. *Circ*. 2004;109:345-350.
54. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E et al: On-pump versus off-pump coronary – artery bypass surgery. *N Engl J Med*. 2009;361:1827-1837.
55. Straka Z, Widimsky P, Jirasek K, Stros P, Votava J, Vanek T et al: Off-pump versus on-pump coronary surgery: final results from a prospective randomized study PRAGUE-4. *Ann Thorac Surg*. 2004;77:789-793.
56. Tully PJ, Baker RA, Kneebone AC, Knight JL: Neuropsychologic and quality-of-life outcomes after coronary artery bypass surgery with and without cardiopulmonary bypass: a prospective randomized trial. *J Cardiothorac Vasc Anethesia*. 2008;22:515-521.
57. Uva MS, Cavaco S, Oliveira AG, Matias F, Silva C, Mesquita A et al: Early graft patency after off-pump and on-pump coronary bypass surgery: a prospective randomized study. *Eur Heart J*. 2010;31:2492-2499.
58. Vedin J, Nyman H, Ericsson A, Hylander S, Vaage J: Cognitive function after on or off pump coronary artery bypass grafting. *Eur J Cardio-Thorac Surg*. 2006;30:305-310.
59. 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 Cardio-Thorac Surg*. 2003;23:917-924.
60. Velissaris T, Tang ATM, Murray M, Mehta RL, Wood PJ, Hett DA et al: A prospective randomized study to evaluate stress response during beating-heart and conventional coronary revascularization. *Ann Thorac Surg*. 2004;78:506-512.
61. Wan IYP, Arifi AA, Wan S, Johnson HY, Sihoe ADL, Thung KH et al: Beating heart revascularization with or without cardiopulmonary bypass: evaluation of inflammatory

response in a prospective randomized study. *J Thorac Cardiovasc Surg*. 2004;127:1624-1631.

62. 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;70:1577-1579.

63. Yu L, Gu T, Shi E, Wang C, Fang Q, Yu Y, Zhao X et al: Off-pump versus on-pump coronary artery bypass surgery in patients with triple-vessel disease and enlarged ventricles. *Ann Saudi Med*. 2014;34:222-228.

63. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ: Assessing the Quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1-12.

64. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al: The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. *Br Med J*. 2011;343:d5928.

65. Almassi GH, Pecsi SA, Collins JF, Shroyer AL, Zenati MA, Grover FL: Predictors and impact of postoperative atrial fibrillation on patients' outcomes: a report from the randomized on versus off bypass trial. *J Thorac Cardiovasc Surg*. 2012;143:93-102.

66. Mao ZF, Zhong XN, Yin JJ, Zhao ZH, Hu XG. Predictors associated with stroke after coronary artery bypass grafting: a systematic review. *J Neurological Sci*. 2015;357:1-7.

67. Kozora E, Kongs S, Collins JF, Hattler B, Baltz J, Hampton M, et al: Cogntive outcomes after on- versus off-pump coronary artery bypass surgery. *Ann Thorac Surg*. 2010;90:1134-1141.

68. Shroyer ALW, Hattler B, Wagner TH, Baltz JH, Collins JF, Carr BM, et al: Comparing off-pump and on-pump clinical outcomes and costs for diabetic cardiac surgery patients. *Ann Thorac Surg.* 2014;98:38-45.

69. UK Department of Health. Reference costs 2014-2015. 2015 available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477919/2014-15_Reference_costs_publication.pdf. Accessed 13th June 2016.
70. Al Ruzzeh S, Epstein D, George S, Bustami M, Wray J, Ilsley C, et al: Economic evaluation of coronary artery bypass grafting surgery with and without cardiopulmonary bypass: cost effectiveness and quality-adjusted life years in a randomized controlled trial. *Artif Organs.* 2008;32:891-897.
71. Lamy AL, Tong W, Devereaux PJ, Gao P, Gafni A, Singh K, et al: The cost implications of off-pump versus on-pump coronary artery bypass graft surgery at one year. *Ann Thorac Surg*. 2014;98:1620-1626.
72. Wagner TH, Hattler B, Bishawi M, Baltz JH, Collins JF, Quin JA, et al: On pump versus off-pump coronary artery bypass surgery: cost-effectiveness analysis alongside a multisite trial. *Ann Thorac Surg*. 2013;96:770-777.

List of Figures and Tables

Figure 1. Post-operative atrial fibrillation

Figure 2. Incidence of Myocardial infarction

Figure 3. ≤30-day mortality

Figure 4. Incidence of stroke

Figure 5. Ventilation time (hours)

Figure 6. ICU stay (days)

Figure 7. Hospital stay (days)

Table 1. Included studies

Supplementary file

Figure S1. Consort statement

Table S1. Excluded randomised controlled studies

Table S2. Evaluation of study quality (modified Jadad scale)