Review

Does off-pump coronary artery bypass reduce the incidence of post-operative atrial fibrillation? A question revisited

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Summary

Atrial fibrillation (AF) is the most common post-operative complication in patients undergoing coronary artery bypass grafting, with an increased incidence associated with advancing age. This study aims to determine whether off-pump coronary artery bypass (OPCAB) reduces the incidence of AF in a generalized patient group (average age < 70 years). A meta-analysis was performed including all randomised and propensity score matched non-randomised studies published between 2001 and 2003 reporting a comparison between the two techniques in a generalized patient group (average age < 70 years). The primary outcome of interest was post-operative AF. Sensitivity analysis was performed to evaluate consistency of the calculated treatment effect. Fourteen studies fulfilled our inclusion criteria, including a total of 16,505 subjects. The incidence of AF was 19% (1612/8265) in the off-pump group versus 24% (1976/8240) in the on-pump group. When considering only the 11 randomised studies (2207 subjects), we found a significant reduction in the incidence of post-operative AF in the off-pump group using a random-effect model (odds ratio (OR) = 0.60, 95% confidence interval (CI) = 0.45–0.82, and chi-square of heterogeneity = 18.02, \( P = 0.05 \)). Sensitivity analysis highlighted one randomised study causing funnel plot asymmetry, exclusion of which resulted in a significant reduction in the incidence of post-operative AF in the off-pump group (OR = 0.71, 95% CI = 0.57–0.90), with a non-significant heterogeneity of 3.91 (\( P = 0.92 \)). When only studies of high quality were considered (898 patients), no significant difference was seen between on and off-pump groups (OR = 0.78, 95% CI = 0.57–1.07, and heterogeneity = 0.53, \( P = 0.91 \)). This may be due to smaller number of patients in this group. Our results suggest that although OPCAB surgery may reduce the incidence of post-operative AF in a generalised population (age < 70 years) this finding is not clearly supported by high quality randomised trials. Although previous evidence suggests that the incidence of post-operative AF is reduced in an elderly population (> 70 years) with off-pump surgery, our results show that the evidence is less clear in a younger population group. The question of whether off-pump surgery in this patient group results in a lower rate of post-operative AF remains to be answered by further high quality randomised research.

Keywords: Atrial fibrillation; Cardiopulmonary bypass; Meta-analysis; Beating heart surgery; Off-pump; Randomised trials; Propensity score matching

1. Background

Atrial arrhythmias are a common post-operative complication amongst patients undergoing coronary artery bypass grafting (CABG) on cardiopulmonary bypass (CPB), with a reported incidence as high as 25–40% [1]. Post-operative atrial fibrillation (AF) has been shown to be associated with morbidity amongst CABG patients, and is therefore an important complication of cardiac surgery. It can also result in thromboembolic complications, additional pharmacotherapy, increased cost, lengthened hospital stay, not to mention the anxiety that this arrhythmia causes the patient [2–4]. Of the patients that experience post-operative AF, those that fail cardioversion (either pharmacological or electrical) face the prospect of oral anticoagulation, and its associated risks.

The exact pathogenesis of post-operative AF in CABG patients is still not understood, and until now it has been impossible to determine whether CPB is in any way related to its generation. Off-pump coronary artery bypass
(OPCAB) offers an important alternative to CPB, and its effect on post-operative AF is yet to be conclusively evaluated. It also provides an opportunity to compare the incidence of AF in patients that have undergone CPB with those who have avoided it altogether.

Meta-analysis can be used as a quantitative method to enhance the precision of estimates of treatment effects, which in this case would mean comparing the incidence of AF following CABG in OPCAB and CPB groups. It is a particularly valuable tool in this instance because it allows for the large number of patients needed in each group that would otherwise be very difficult to obtain in a large-scale high quality randomised trial. A meta-analysis is however only as good as the studies it includes and the factors it takes into account.

In a recent meta-analysis of studies comparing OPCAB and CPB, a statistically significant reduction in post-operative AF has been reported with OPCAB [5]. On closer review of these results, we feel there are three issues that need to be raised: first, this analysis did not include many recent randomised trials comparing the two techniques. Second, the authors did not seem to sufficiently explore the possible causes for heterogeneity identified between the studies. An example of this is the selection criteria used for patient allocation to each technique, something that can only be matched for by meta-analysing studies of prospective randomised or retrospective propensity matched design. Third, the analysis did not consider the association of AF with age and other risk factors. This latter point is important because by including studies containing elderly or high-risk patients [6,7], they have produced a more clinically heterogeneous patient group. Finally, it has been suggested that in meta-analysis of observational study data, we should focus on explaining the causes for heterogeneity rather than calculating the overall estimates for several outcomes of interest [8].

In a recently published paper, we have shown a significant reduction in the incidence of post-operative AF with OPCAB in an elderly (>70 years) population [9]. This study aims to assess whether OPCAB reduces the incidence of AF in a generalized patient population (average age <70 years) undergoing CABG when compared to traditional (CPB) techniques. We plan to do this by meta-analysing the ‘best available evidence’ in the published literature including randomised trials and the highest quality observational studies comparing the incidence of AF in OPCAB versus CPB patients undergoing CABG, whilst taking into account the factor of age of patients selected in each group.

2. Methods

2.1. Study selection

A Medline search was performed on all randomised trials reporting on patients undergoing CABG and comparing OPCAB and CPB techniques. The following Mesh search headings were used: ‘randomised controlled trials’, and ‘cardiopulmonary bypass’ or ‘off-pump’, ‘coronary artery bypass methods’ and ‘atrial fibrillation’. We also performed a Medline search of studies comparing OPCAB and CPB using propensity analysis with the keywords ‘off-pump and propensity’. The ‘related articles’ function was used to broaden the searches, and all abstracts, studies, and citations scanned were reviewed. Using these strategies, randomised and propensity score matched (PSM) studies comparing OPCAB and CPB were identified and data regarding the outcome of interest (AF) extracted.

2.2. Data extraction

Two reviewers (A.T. and A.O.), independently extracted the following data from each study: first author, year of publication, study population characteristics, study design, inclusion and exclusion criteria, number of subjects operated on with each technique, and conversion rate from OPCAB to CPB. Meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the quality of reporting of meta-analyses (QUORUM) guidelines for reporting of meta-analyses [10,11].

The quality of the randomised studies was also evaluated using criteria proposed by Heyland et al. [12,13] and graded on an ordinal 14-point scale with higher scores representing studies of higher quality. Parameters used in this grading system include: randomisation, blinding, intention to treat, patient selection, compatibility of compared groups, extent of follow-up, description of treatment protocol, co-interventions, and description of outcomes. Each study was graded as follows: Level 1 (1–5 marks), Level 2 (6–10 marks), and Level 3 (11–14 marks). Using this system, Level 3 studies were deemed to be of higher quality than Level 1. For practical purposes, PSM studies were classified as Level 1 (poor quality).

To compare the two groups, we focused on variables that have previously been associated with AF namely age, gender, hypertension, diabetes, ejection fraction, chronic obstructive pulmonary disease and advanced coronary artery disease (left main stem, three vessel disease, and re-operation). The distribution of these variables between OPCAB and CPB groups is presented in Table 1.

2.3. Inclusion and exclusion criteria

In order to enter our analysis, studies had to:

1. Be prospective randomised or PSM observational studies comparing OPCAB and CPB techniques.
2. Compare the two techniques in a generalised patient group (average age <70 years).
3. Contain a previously unreported patient group (if patient material was reported more than once, we chose the most informative and recent article).
4. PSM studies that did not report the AF specifically for the outcome of interest in both OPCAB and CPB groups.

3. They displayed a zero for the outcome of interest in both OPCAB and CPB groups. This outcome was identified as 'atrial arrhythmia' was used. Other types of arrhythmias (i.e. ventricular) were excluded from our analysis. It is important to note that the studies selected for this analysis reported 'new onset' post-operative AF and thus by definition excluded patients with pre-existing AF. We appreciate that different studies may have varying definitions of AF (intermittent or persistent), type and duration of patient monitoring, and protocols for prophylaxis (i.e. the use of beta-blockers), but it was not the interest of our study to differentiate between these differing practices. Finally, the role of magnesium supplementation in patients undergoing cardiac surgery has been described for both OPCAB and CPB techniques [15]. The studies included in our meta-analysis did not mention magnesium replacement.

2. The development of post-operative AF was the only outcome of interest in one of the two groups [16,17]. These ‘zero cells’ create problems with the computation of ratio measures and its standard error of the treatment effect. This can be resolved by adding the value 0.5 in each cell of the 2 × 2 table for the study in question, and if there are no events for both OPCAB and CPB groups the study should be discarded from the meta-analysis.

2.5. Statistical analysis

This was carried out using the odds ratio (OR) as the summary statistic. This ratio represents the odds of an adverse event occurring in the treatment (OPCAB) group compared with the reference (CPB) group. An OR of less than one favours the treatment group, and the point estimate of the OR is considered statistically significant at the P < 0.05 level if the 95% confidence interval (CI) does not include the value one. Aggregation of the overall rates of the outcomes of interest was performed with the Mantel-Haenszel Chi-square test. Yate’s correction was used for calculating the overall treatment effect in each study is the same, whereas in a random-effect model it is assumed that there is variation between studies and the calculated OR thus has a more conservative value [18,19]. For surgical research, meta-analysis using the random-effect model is preferable particularly because patients that are operated on in different centres have varying risk profiles and selection criteria for each surgical technique.

In the tabulation of our results (Figs. 1 and 2), squares indicate point estimates of treatment effect (OR), with the size of the square representing the weight attributed to each study. Studies were excluded from our analysis if:

1. The surgical technique (whether OPCAB or CPB) could not be defined.
2. The development of AF with both techniques was not reported or it was impossible to calculate this from the published results.
3. They displayed a zero for the outcome of interest in both OPCAB and CPB groups.
4. PSM studies that did not report the AF specifically for the sample group were excluded from the meta-analysis [14].

Table 1

| Author (total number of patients) | Hypertension | Re-operation | COPD | Diabetes | Ejection fraction | Female gender | Left main stem or three vessel disease |
|----------------------------------|--------------|--------------|------|----------|------------------|--------------|-------------------------------------|
|                                  | OPCAB | CPB   | OPCAB | CPB | OPCAB | CPB | OPCAB | CPB | OPCAB | CPB | OPCAB | CPB | OPCAB | CPB | OPCAB | CPB |
| 1. Angelini (221) | 122 | 99 | EX | EX | EX | EX | 51 | 44 | 44(c) | 44(c) | 336 | 35 | ND | ND |
| 2. Czerny (80) | ND | ND | EX | EX | ND | ND | 37 | 35 | 11(b) | 7(b) | 33 | 36 | ND | ND |
| 3. Muneretto (176) | ND | ND | EX | EX | 10 | 11 | 37 | 35 | 11(b) | 7(b) | 33 | 36 | 8(d) | 10(d) |
| 4. Puskas (197) | 64 | 61 | EX | EX | 10 | 8 | 32 | 33 | 23(c) | 24(c) | 22 | 23 | ND | ND |
| 5. Smith (44) | 13 | 15 | EX | EX | ND | ND | 2 | 4 | 3(b) | 2(b) | 3 | 4 | ND | ND |
| 6. Van Dijk (281) | 57 | 61 | EX | EX | 13 | 14 | 13 | 24 | 33(c) | 29(c) | 48 | 42 | 28(e) | 38(e) |
| 7. Zamvar (60) | ND | ND | EX | EX | ND | ND | ND | ND | ND | ND | ND | ND |
| 8. Gerola (160) | 37 | 43 | EX | EX | EX | EX | 19 | 14 | 0(b) | 0(b) | 29 | 26 | EX | EX |
| 9. Legare (300) | 105 | 90 | EX | EX | 25 | 21 | 44 | 54 | 20(c) | 23(c) | 28 | 31 | ND | 111(e) |
| 10. Straka (388) | 114 | 109 | 2 | 4 | ND | ND | 57 | 53 | 8(b) | 9(b) | 47 | 26 | 139(e) | 125(e) |
| 11. Lingaas (120) | 25 | 26 | ND | ND | 5 | 10 | 8 | 12 | 71(a) | 72(a) | 9 | 17 | 33(e) | 27(e) |
| 12. Karthik (828) | 219 | 178 | 18 | 24 | 105 | 99 | 76 | 63 | 44(b) | 62(b) | 127 | 99 | 299(e) | 341(e) |
| 13. Mack (11,548) | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| 14. Calafiore (1922) | ND | ND | 15 | 17 | 58 | 52 | 22.6 | 21.6 | 58.3(a) | 57.1(a) | 161 | 162 | 316(e) | 358(e) |

ND, not documented; EX, excluded; COPD, chronic obstructive pulmonary disease. (a) Mean ejection fraction (%). (b) Ejection fraction equal or <30% and equal or <35%. (c) Ejection fraction equal or <50% or equal or <45%. (d) Left main stem disease. (e) Three vessel disease. Bold numbers indicate statistically significant differences between groups (P < 0.05).
study and 95% CI indicated by horizontal bars. The diamond represents the summary OR from the pooled studies with 95% CI.

Analysis was conducted by using the statistical software SPSS version 10.0 for Windows (SPSS, Inc., Chicago, IL), Intercooled Stata version 7.0 for Windows (Stata Corporation, USA), Review Manager Version 4.2 (The Cochrane Collaboration, Software Update, Oxford) and the Sample Power 2.0 (SPSS, Inc., Chicago, IL) for power analysis calculations.

The strategies we employed to quantitatively assess heterogeneity were:

1. Statistical tests—re-analysing data with two different statistical approaches using a random and a fixed-effect model.
2. Graphical exploration—using funnel plots to evaluate publication bias [20,21].
3. Sensitivity analysis by subgroup analysis.

In order to do this, the following variables were evaluated: study size (those with more than 50 patients in each group), use of hypothermic CPB, use of cold blood cardioplegia, symmetry in funnel plot, study quality and recent year of publication (excluding studies before 2002 when the technique may have been less developed).

We also calculated the following parameters: absolute risk reduction (ARR) which is the difference in the incidence of AF between OPCAB and CPB groups, and number needed to treat (NNT) which is the number of patients who must be treated (in this case to be operated by using OPCAB technique) in order to prevent one event of AF ($NNT = 1/ARR$).

### 2.6. Sample size considerations

The incidence of AF in CPB patients (Fig. 1) was calculated to be approximately 24% (1976/8240). In order to rule out a 30% relative risk reduction (from 24 to 17%) with a 5% significance level and 90% power, a traditional randomised controlled trial would require 726 patients in each arm.

### 3. Results

#### 3.1. Selected studies

We identified 96 studies using the keywords ‘off-pump and randomised’ and 15 studies using off-pump and propensity. The search was further refined using the previously mentioned selection criteria, with 14 studies identified reporting the incidence of post-operative AF in OPCAB versus CPB groups, all published between 2001 and 2004 [21–34]. Of these 11 were of randomised prospective design and 3 were PSM studies. These 14 studies were included in our final analysis and in total contained 16,505 subjects, of which 8265 (50%) underwent OPCAB and 8240 (50%) underwent CPB (Table 2).

On review of the data extraction, there was 100% agreement between the two reviewers and the agreement on quality score of the individual studies was also high.

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**Fig. 1. Meta-analysis of all the studies (OPCAB versus CPB) comparing incidence of post-operative atrial fibrillation.**

| Study | Treatment | Control | OR (random) | Weight | OR (random) | Year |
|-------|-----------|---------|-------------|--------|-------------|------|
| ANGILO | 25/200 | 74/201 | 8.63 | 0.25 (0.15, 0.41) | 2002 |
| CZERNY | 5/60 | 7/60 | 2.39 | 0.19 (0.33, 1.15) | 2001 |
| GEROLA | 4/80 | 7/80 | 2.29 | 0.19 (0.33, 1.15) | 2003 |
| LEGARE | 39/150 | 49/150 | 8.51 | 0.72 (0.44, 1.19) | 2004 |
| LINGAS | 18/60 | 20/60 | 5.07 | 0.48 (0.22, 0.93) | 2003 |
| MUNIETTO | 19/88 | 21/88 | 6.12 | 0.51 (0.26, 0.99) | 2003 |
| PUSKAS | 16/99 | 22/99 | 5.62 | 0.48 (0.23, 1.07) | 2003 |
| SMITH | 5/21 | 6/23 | 2.01 | 0.39 (0.07, 0.80) | 2002 |
| STRAKA | 41/204 | 44/204 | 8.89 | 0.98 (0.49, 1.87) | 2004 |
| VAN Dijk | 20/142 | 21/139 | 6.21 | 0.39 (0.17, 0.87) | 2001 |
| ZAMVAR | 4/30 | 10/30 | 2.21 | 0.31 (0.06, 1.73) | 2002 |

Total events: 156 (Treatment), 290 (Control)

Test for heterogeneity: $\chi^2 = 18.02$, df = 10 ($P = 0.05$), $I^2 = 44.5$

Test for overall effect: $Z = 3.28$ ($P = 0.001$)

**3.2. Propensity score matched studies**

| Study | Treatment | Control | OR (random) | Weight | OR (random) |
|-------|-----------|---------|-------------|--------|-------------|
| CALAFIORE | 102/941 | 130/941 | 7.03 | 0.39 (0.20, 0.80) | 2003 |
| KARAKI | 110/417 | 97/417 | 12.28 | 1.16 (0.65, 2.08) | 2003 |
| MAIZ | 1203/5774 | 1323/5774 | 16.68 | 0.79 (0.70, 0.87) | 2004 |

Total events: 156 (Treatment), 290 (Control)

Test for heterogeneity: $\chi^2 = 7.83$, df = 2 ($P = 0.02$), $I^2 = 54.5$

Test for overall effect: $Z = 1.00$ ($P = 0.13$)

Total events: 1812 (Treatment), 1816 (Control)

Test for heterogeneity: $\chi^2 = 3.54$ ($P = 0.0004$)
The weighted Kappa is 0.94. The majority of the randomised studies were ranked at Level 2 (moderate quality) with four studies at Level 3 (high quality) [21,23,29,31]. The 3 PSM studies [32–34] were ranked at Level 1 (low quality). Of the 14 studies (Table 2) 10 reported the conversion rate from OPCAB to CPB (range 0–22.5%).

All the studies contained groups that were comparable for COPD and diabetes, although two studies did not contain OPCAB and CPB groups matched for sex [25,30]. When considering the other risk factors for post-operative AF, the incidence of pre-operative hypertension was not comparable between the two groups in two studies [25,32], ejection fraction in one study [32] and extent of coronary disease in one study [32]. Re-do operations were included in only three studies [30,32,34]. One study defined the outcome of interest as atrial arrhythmia [32], whereas in the remainder atrial fibrillation was clearly stated.

3.2. Meta-analysis

Four out of the 14 studies showed a statistically significant difference between the two groups in the incidence of AF [24,25,33,34]. Taking all studies into account, this was 19% (1612/8265) in the OPCAB group versus 24% (1976/8240) in the CPB group. Using the random-effect model (Fig. 1), we calculated an OR of 0.69 (95% CI 0.56–0.85) and a chi-square of heterogeneity of 32.6 (P = 0.002). Using a fixed-effect model, the OR was calculated as 0.77 (95% CI 0.71–0.83) with identical heterogeneity.

When we focused only on the 11 randomised studies (2207 subjects) meta-analysis using the random-effect model revealed an OR of 0.60 (95% CI 0.45–0.82), and chi-square of heterogeneity of 18.02 (P = 0.05). Using a fixed-effect model for all the randomised studies the OR was calculated as 0.58 (95% CI 0.48–0.72) with identical heterogeneity.

3.3. Sensitivity analysis results

We identified significant differences in the OR and heterogeneity for the outcome of interest (AF), when comparing random and fixed-effect models, with further investigation being undertaken by graphical exploration.
Inclusion criteria: 1. informed consent; 2. elective CAbb; 3. severe obstructive pulmonary disease; 4. normal ejection fraction; 5. multi-vessel disease; 6. no diffuse coronary disease; 7. no ventricular hypertrophy; 8. no cardiac enlargement; 9. low risk patients; 10. no significant renal dysfunction; 11. LAD lesion equal or more than 70%; 12. associated lesion in the RCA; 13. vessel size 30%; B, recent MI within 1 month or 6 weeks; C, history of supraventricular tachycardia; D, previous CAbb; E, previous stroke; F, previous TIA; G, coagulopathy; H, anatomy of the Cx (distal stenoses); I, renal impairment; J, respiratory impairment; K, patients in cardiogenic shock; L, patient requiring IABP preoperatively; M, patients requiring emergency surgery; N, need for other concomitant operation; O, propensity score matching)

Further subgroup analysis showed that when we included studies of high quality (898 patients), the OR for incidence of AF (Fig. 3) changed significantly to 0.78 (95% CI 0.57–1.07), with a heterogeneity of 0.53 (P = 0.91). Two of the studies were published before 2002 [21,26] and on their exclusion the calculated OR for the incidence of AF changed to 0.67 (95% CI 0.54–0.84), with a significant heterogeneity of 32.27 (P = 0.0007). Three studies were of small size (<50 patients in each group) [22,26,27] and exclusion of these from the analysis resulted in a calculated OR for incidence of AF of 0.70 (95% CI 0.56–0.87), with a significant heterogeneity of 30.60 (P = 0.0007).

Hypothermic CPB was not used in four studies [25,26,30,34] and was not reported in one study [33]. Exclusion of these five studies from the analysis resulted in a calculated OR for incidence of AF of 0.81 (95% CI 0.63–1.03), with heterogeneity of 9.67 (P = 0.29). Similarly, cold blood cardioplegia was not used in four studies [21,22,29,30] and not reported in one study [33]. When we excluded these five studies from the analysis the calculated OR for incidence of AF changed to 0.59 (95% CI 0.41–0.83), with heterogeneity of 29.06 (P = 0.0003). Retrograde cardioplegia was used in four studies [23,24,26,32,33] and was not reported in one [33]. On exclusion of these five studies from the analysis the calculated OR for incidence of AF changed to 0.61 (95% CI 0.45–0.84), with heterogeneity of 17.79 (P = 0.02).
4. Discussion

The results of our meta-analysis suggest that OPCAB surgery may reduce the incidence of post-operative AF in a generalized population (mean age < 70 years) when compared to CPB techniques. When considering only the data from the randomised trials, we identified a significant reduction in the incidence of post-operative AF in the OPCAB group with OR of 0.71 (95% CI 0.57–0.90) without significant heterogeneity (3.91, P = 0.92) between studies. Our results have further investigated a potentially important link between off-pump cardiac surgery and the incidence of post-operative AF, and highlighted the factors that need to be taken into account when meta-analysing randomised and non-randomised studies. Where only studies of high quality were considered, non-significance may have been achieved as a result of small number of patients in the selected group.

In a previous meta-analysis of non-randomised studies comparing OPCAB and CPB in an elderly (> 70 years) patient group, we have already shown a reduced incidence in post-operative AF with OPCAB [6]. The calculated OR for post-operative AF with OPCAB in the generalized population was very similar to that which we have previously found in an elderly population (OR = 0.70, 95% CI 0.56–0.89). For the elderly, an ARR of 3% and NNT of 33 had been calculated, whereas in this paper with a generalized population, the maximum value of the OR favouring the treatment (OPCAB) group was 0.90 (within 95% CI), translating to a relative risk reduction of at least 10%. For the studies included in our analysis, the average incidence of AF in CPB patients was 24%. Therefore, a 10% reduction in this would translate to an incidence of AF with OPCAB of 21.6%. The calculated ARR would be approximately 2.5% with OPCAB, meaning the NNT would be 40. The NNT would be significantly higher in patients at low-risk of AF (age < 70 years, no hypertension, COPD, or diabetes, preserved left ventricular function and without advanced coronary artery disease).

Age has shown to be the strongest independent predictor of post-operative AF, probably due an increased incidence of atherosclerosis, hypertension, diabetes, and reduced cardiopulmonary reserve in older patients [35]. Our results suggest that OPCAB has a beneficial effect on the incidence of AF in a generalised patient group, although this seems to be more marked in the elderly (age > 70 years). The factors relating to CPB that may be important in the generation of post-operative AF include ischaemia during cardioplegic arrest and cannulation technique [2]. Both of these problems should in theory be avoided in OPCAB. Evidence that CPB has an immunological effect on the degree of inflammatory response and complement activation may also be important in the generation of this post-operative arrhythmia [36].

In a previous meta-analysis, we have emphasized the importance of taking into consideration the selection criteria for treatment allocation, comparability between treatment groups and assessment of outcome as tools to evaluate the quality of observational studies [37]. Many factors influence the type of treatment that patients receive in a non-randomised observational study, with physicians selecting the treatment modality for a particular patient based on his or her characteristics (age, severity of disease, type of anatomy, etc.). PPM is a useful statistical technique designed to reduce selection bias in order to achieve
‘randomization after the fact’ [38]. Randomised studies are considered to be the highest level of evidence for comparing a treatment with a control, and have the essential feature of some random mechanism controlling treatment assignment thereby limiting patient selection bias.

Investigating heterogeneity between studies is more significant than a simple calculation of an overall estimate. Results from meta-analysis where there is significant heterogeneity between studies can be misleading. Study design, size, varying inclusion and exclusion criteria, and comparability between OPCAB and CPB groups are as important as patient characteristics and surgical skill. These must all therefore be taken into account before drawing any conclusions and suggesting change to clinical practice. When statistical heterogeneity has been identified between randomised trials it is likely to be because of the underlying clinical heterogeneity or less often due to chance. It is important to bear in mind, however, that even meta-analysis without significant heterogeneity can never be interpreted as direct evidence in favour of the null hypothesis of homogeneity. This is because tests that look for heterogeneity have low power in detecting even a moderate degree of genuine heterogeneity as being statistically significant [39].

We have also found that varying myocardial protection strategies and systematic temperature during CPB can alter the calculated OR and heterogeneity between studies for post-operative AF. These factors can thus be significant covariates when OPCAB and CPB are compared and should be taken into account when designing future studies evaluating the incidence of AF following CABG. The effect of normothermia and varying cardioplegic techniques on the requirements for cardiac support has not as of yet been adequately assessed.

Although our results highlight an important message, we acknowledge the limitation of our statistical analysis. First, it was based on small, randomised trials, and thus must be treated with caution. Second, we appreciate that in different studies, operations were performed by different surgeons with different equipment, conduits, and anaesthetic techniques, all of which increases the clinical heterogeneity in the patient group. Third, other intra-operative variables such as the type of incision used for coronary revascularisation, and the learning curve associated with the newer OPCAB technique must also be taken into account. This is particularly important in re-do operations which were included in a limited proportion of the trials used in our meta-analysis. Fourth, we did not assess the effect of several post-operative variables such as pulmonary complications (which can cause significant hypoxaemia), post-operative bleeding, and pericardial tamponade. The latter can lower cardiac output, increasing inotropic requirements, resulting in sympathetic activation with subsequent increase in the incidence of post-operative AF. Finally, we acknowledge that the reported incidence of new post-operative AF in the studies we meta-analysed depends to some extent on the type and duration of post-operative arrhythmia monitoring, which may have varied between studies.

It is important to recognise that two studies selected for our analysis caused significant heterogeneity in our results [25,32]. The first of these reported a significantly higher incidence of post-operative AF in the CPB group (49%) as compared to OPCAB (14%) [25]. The effect that this study caused on our meta-analysis is well illustrated by the asymmetry in the funnel plot (Fig. 1). The non-uniformity of post-operative management in this study has previously been questioned [2], and would certainly account for the heterogeneity caused by its results. In particular, patients in the CPB group of this study had a greater requirement for inotropes and higher incidence of pulmonary complications when compared to the OPCAB group, both of which are associated with an increased risk of post-operative AF [40].

The second study [32] was not excluded from our analysis because it lay very close to the 95% confidence lines on the funnel plot. This illustrates the use of the funnel plot to detect outlier studies and help direct the sensitivity analysis in order to develop a more robust model. The fact that this study causes heterogeneity in our meta-analysis may be explained by the fact that they contained a patient group undergoing mainly emergency as opposed to elective revascularisation. There were also comparable differences between the OPCAB and CPB groups in this study, and as previously mentioned, the definition for the outcome of interest was atrial ‘arrhythmia’ as opposed to ‘fibrillation’.

Advances in OPCAB surgery have meant that it now challenges conventional CABG with CPB as the first-line operation for coronary revascularisation. Although theoretical benefits of avoiding an extracorporeal circuit as in CPB seem to support OPCAB surgery, there is at present no clear evidence as to which patient groups will benefit most from the seemingly more physiological off-pump strategy. With regards to the generation of AF after CABG, we have identified a broader patient group that may benefit from OPCAB surgery. The results of this meta-analysis add voice to the call for a large-scale multi-centre randomised trial of OPCAB versus CPB with the development of post-operative AF as a primary endpoint. This may be the only definitive way answer the question of whether OPCAB reduces the incidence of post-operative AF in patients undergoing CABG.

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