Wiley
Journal of Cardiac Surgery
Volume 2024, Article ID 3616580, 13 pages
https://doi.org/10.1155/2024/3616580

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Research Article

Short- and Midterm Outcomes of Off- and On-Pump Coronary Artery Bypass in Patients with a Mean Age of 65 or More: Systematic Review and Meta-Analysis

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Received 17 May 2024; Revised 15 July 2024; Accepted 24 July 2024

Academic Editor: Ki-Bong Kim

Background. Advancing age is a nonmodifiable risk factor for the development of coronary artery disease. Furthermore, patients >65 years old are considered at high risk for coronary artery bypass grafting (CABG). The aim of this study was to investigate whether there were any differences in clinical outcomes for patients with a mean age ≥65 undergoing CABG on or off pump. *Methods*. Systematic searches were conducted in EMBASE, PubMed, Web of Science, and Cochrane Central Registry of Controlled Trials (CENTRAL). The key search terms used were "cardiopulmonary bypass" OR "On pump" AND "off pump" OR "beating heart" AND "coronary artery bypass grafting" OR "CABG" AND "age." This was followed by a meta-analysis assessing the primary outcomes mortality, myocardial infarction, renal failure, and stroke in the short—(30 days) and midterm (12–44 months) and repeat revascularisation at midterm follow up. Secondary outcomes investigated included postoperative atrial fibrillation, number of units of blood transfused, ventilation time, length of intensive care unit stay, and length of hospital stay. *Results*. 14 studies involving 10,260 participants, 5,141 of whom had on-pump CABG and 5,119 of whom had off-pump CABG were identified. There was a significantly greater need for repeat revascularisation in the off-pump group (risk ratio 1.47, 95% confidence interval 1.07 to 2.01, $I^2 = 0\%$, $p = 0.02$) at midterm follow up. The off-pump group also had a shorter hospital stay. All other comparisons were insignificant. *Conclusion*. A number of different factors contribute to whether the increased need for repeat revascularisation for off-pump patients is truly clinically significant. This requires further investigation in meta-analysis based on longer-term trials in patients with a mean age ≥65. Otherwise, the similarity in clinical outcomes for patients in this age group suggests the choice to carry out CABG on or off pump should continue to be at the surgeon's discretion.

1. Introduction

Advancing age is considered one of the major nonmodifiable risk factors for the development of coronary heart disease [1] with cardiovascular ageing involving both intra- and extracardiac dysfunction [2]. This opens debate as to the best revascularisation approach for the older patient with symptomatic angina. According to the National Institute for Health and Care Excellence (NICE), the survival benefit of coronary artery bypass grafting (CABG) compared to percutaneous coronary intervention (PCI) should be considered for patients over 65 years of age [3].

This raises the question as to whether CABG in this older population should be carried out off or on pump (without/with cardiopulmonary bypass). There have been many randomized clinical trials (RCTs) investigating the question of which is superior, but these have mostly been carried out in patients with an average age <65 [4], without the increased likelihood of comorbidities that make the ≥65 s more vulnerable [1] and in the short term [4]. Long-term data for ≥65 s is sparse but one meta-analysis of RCTs in a mixed-age population showed a survival benefit for the on-pump technique [5].

Different outcomes following off- or on-pump CABG in the elderly population have been investigated in some previous meta-analyses. Nearly all of these studies are dated (e.g., [6]), concentrate either exclusively on the >70 s [7] or >80 s [8] and examine retrospective clinical trials [6, 8]. The exception to this is a meta-analysis published last year examining 5 RCTs featuring patients >65 [9]. There are, however, several (9 more, making a total of 14) more RCTs available for analysis. Therefore, the aim of the current meta-analysis is to assess the early and midterm outcomes of off- vs on-pump CABG in patients with a mean age ≥65. The hypothesis investigated is that off-pump CABG may be beneficial in these older patients.

2. Methods

This meta-analysis involves pooling of already published data and therefore does not require ethical approval. This systematic review and meta-analysis followed the PRISMA method (see Suppl. file for completed checklist).

2.1. Literature Search Strategy. Systematic searches were carried out in EMBASE, PubMed, Web of Science, and the Cochrane Central Registry of Controlled Trials (CENTRAL) to identify RCTs. The search was supplemented by scanning the reference lists of included trials. The key search terms used were "cardiopulmonary bypass" OR "On pump" AND "off pump" OR "beating heart" AND "coronary artery bypass grafting" OR "CABG" AND "age" (see Figure S1 for the search strategy). 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 31 st, 2024.

2.2. Eligibility Criteria. The types of studies to be included comprised RCTs of adults with a mean age ≥65 years undergoing CABG either without (off pump) or with (on pump) cardiopulmonary bypass. There were no language restrictions. Animal studies, review papers, and non-randomized controlled trials were excluded. Patients with coronary artery disease (CAD) who were treated by other modalities, e.g., PCI were also excluded. This meta-analysis considered all studies reporting the short- and/or midterm outcomes from RCTs where patients with a mean age ≥65 years with stable angina or acute coronary syndrome being treated with CABG were exposed to either off pump or on pump. The primary outcomes were mortality, myocardial infarction, renal failure and stroke in both the short and midterm and repeat revascularisation in the midterm. Secondary outcomes in the short term were incidence of postoperative atrial fibrillation (AF), number of units of blood transfused, ventilation time, length of intensive care unit (ICU), and hospital stay.

2.3. Data Extraction and Critical Appraisal. Data were extracted into predesigned tables (JET, NK). This was checked by TFE with any conflicts resolved by NAS. Study quality/risk of bias was analysed using the tool provided in RevMan Web. Publication bias was analysed using funnel plots [10].

2.4. Statistical Analysis. This analysis includes both continuous and dichotomous data. The former was investigated by mean difference, whereas the latter was calculated using risk ratios (RR). An RR is a ratio of the risk of an event occurring in one group compared to the risk of the event occurring in the other group. All analyses were conducted using RevMan Web (Nordic Cochrane Centre, Denmark). A random effects inverse variance model was used throughout. Heterogeneity was quantified using the Cochrane Q test [11]. We used a 5% level of significance and 95% confidence intervals; forest and funnel plots were produced using RevMan Web.

3. Results

The 14 studies included had an aggregate of 10,260 participants, 5,141 of whom had on-pump CABG and 5,119 of whom had off-pump CABG (see Figure 1). One study contains 2 subgroups [12]. That is one group with cell saver blood transfusion and one group without. Two studies are duplicated because the outcomes at 30 days and midterm follow up were reported in separate papers [13–16]. As short- and midterm outcomes are analysed separately, duplication of data are never found in a single forest plot. Suppl. Table 1 lists the excluded studies, and reasons for their exclusion.

Table 1 summarizes the characteristics of the included studies [12–27], as well as patient comorbidities. Six studies reported midterm follow up data. Three of the studies with midterm follow up reported that the surgeons were experienced [14, 16, 18], whereas their experience was not mentioned in the other three papers with midterm follow up [18, 24, 26]. A significantly lower number of grafts were performed in 4 of the studies with midterm follow up [14, 18, 21], whereas the difference was not significant in the other 3 studies with midterm follow up [16, 24, 26]. Reporting on the completeness of revascularisation in the studies with midterm follow up was mixed. Two of the studies do not mention the completeness of revascularisation [21, 24]. Nesher et al. [18] and Sharma et al. [26] report that the number of patients receiving fewer than expected grafts was greater in the off-pump group. Lamy et al. [13] report that the completeness of revascularisation was lower in the off-pump group, although $p = 0.05$ for the comparison. Finally, Møller et al. [15] report no difference in the completeness of revascularisation between the two groups. None of the studies with midterm follow up reported how repeat revascularisation if required was carried out, nor the reason for it.

3.1. Summary of Results. Table 2 summarizes all of the results obtained for the different comparisons in this meta-analysis.

3.2. Assessment of Primary and Secondary Outcomes: Short-Term Primary Outcomes at 30 Days-Mortality. Ten studies reported the incidence of mortality within 30 days. The risk

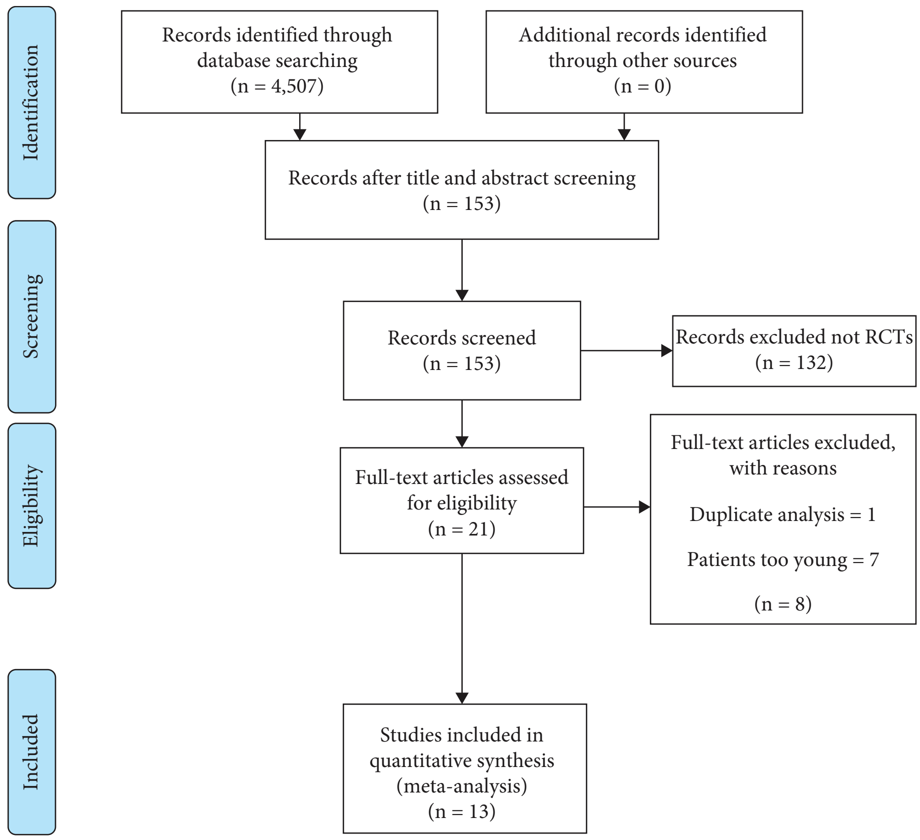

Figure 1: Consort figure.

ratio (RR) for the comparison was 0.83 (95% confidence interval [CI] = 0.64 to 1.06; $I^2 = 0\%$; $P = 0.13$) (Figure 2(a)). The risk of dying 30 days postsurgery was not significantly different between the two groups. The funnel plot was asymmetrical (Suppl. file Figure S3).

3.3. Myocardial Infarction. Ten studies reported the incidence of myocardial infarction within 30 days. The RR for the comparison was 0.92 (95% CI = 0.73 to 1.15; $I^2 = 10\%$; $P = 0.47$) (Figure 2(b)) The risk of having a myocardial infarction 30 days postsurgery was not significantly different between the two groups. The funnel plot was asymmetrical (Suppl. file Figure S4).

3.4. Renal Failure. Eight studies reported the incidence of renal failure within 30 days. The RR for the comparison was 0.82 (95% CI = 0.61 to 1.10; $I^2 = 0\%$; $P = 0.18$) (Figure 2(c)). The risk of having renal failure 30 days postsurgery was not significantly different between the two groups. The funnel plot was asymmetrical (Suppl. file Figure S5).

3.5. Stroke. All studies reporting short term outcomes (13 studies, 14 intervention groups) reported the incidence of stroke within 30 days. The RR for the comparison was 0.80 (95% CI = 0.60 to 1.07; $I^2 = 0\%$; $P = 0.14$) (Figure 2(c)). The risk of having a stroke within 30 days of surgery was not significantly different between the two groups. The funnel plot was asymmetrical (Suppl. file Figure S6).

3.6. Midterm Primary Outcomes: Mortality. All of the studies assessing midterm follow up reported mortality. The RR for the comparison was 1.08 (95% CI 0.87 to 1.34, $I^2 = 24\%$, $p = 0.47$) (Figure 3(a)). The risk of dying by the midterm follow up was similar in the on- and off-pump groups. The funnel plot was asymmetrical (Suppl. file Figure S7).

3.7. Myocardial Infarction (MI). All of the studies assessing midterm follow up reported the incidence of MI. The RR for the comparison was 0.85 (95% CI 0.71 to 1.01, $I^2 = 0\%$, $p = 0.07$) (Figure 3(b)). There was no significant difference in the risk of suffering an MI by the midterm follow up. The funnel plot was asymmetrical (Suppl. file Figure S8).

3.8. Renal Failure. Four studies reported the occurrence of new renal failure at midterm follow up. The RR was 0.84 (95% CI 0.62 to 1.15, $I^2 = 0\%$, $p = 0.28$) (Figure 3(c)). There was no difference in the risk of developing renal failure between the two groups. The funnel plot was asymmetrical (Suppl. file Figure S9).

3.9. Stroke. All of the studies reported the incidence of stroke at midterm follow up. The RR for the comparison was 0.87 (95% CI 0.67 to 1.13, $I^2 = 0\%$, $p = 0.31$) (Figure 3(d)). The risk of having a stroke was similar in the two groups. The funnel plot was asymmetrical (Suppl. file Figure S10).

Table 1: Characteristics of included studies.

Study	No. on (off)	Age years on (off)	Male % on (off)	Comorbidities % on (off)	Length of follow up (mo)	No. of grafts (mean ± SD) on (off)	Experience of surgeons	Outcome measures
Carrier et al. [19] Canada	37 (28)	70 ± 6 (70 ± 8)	84 (78)	*Anaemia*- 16 (32) *COPD*- 22 (25) *Diabetes mellitus*- 46 (50) *Hypertension*- 81 (82)	N/A	3.4 ± 1 (3 ± 1)	Several years	Bleeding Blood transfusion Hospital stay ICU stay MI Mortality Renal insufficiency Stroke
Diegeler et al. [20] Germany	1207 (1187)	78.4 ± 2.9 (78.6 ± 3.0)	68 (69)	*Diabetes mellitus*- 13.8 (15.1) *Dialysis*- 0.9 (0.9) *Previous MI*- 37.8 (36) *Previous PCI*- 21.8 (22.6) *Previous stroke*- 7.9 (10.2)	12	2.8 (2.7) ($p < 0.001$)	Average no. of previous surgeries: On: 1378; off: 514	Hospital stay ICU stay MI Mortality New renal-replacement therapy Stroke Ventilation time
Hlavicka et al. [21] Czech republic	108 (98)	73.6 ± 7.4 (74.7 ± 6.5)	57.4 (59.2)	*Diabetes mellitus*- 46.3 (48) *Hypertension*- 83.3 (83.7) *Previous MI*- 67.6 (59.2) *Previous PCI*- 21.3 (22.4) *Previous stroke*- 12 (16.3)	12	2.66 (2.04) ($p < 0.0011$)	Not mentioned	MI Mortality Renal failure Stroke

Table 1: Continued.

Study	No. on (off)	Age years on (off)	Male % on (off)	Comorbidities % on (off)	Length of follow up (mo)	No. of grafts (mean ± SD) on (off)	Experience of surgeons	Outcome measures
Houlind et al. [22] Denmark	450 (450)	75 (75)	78 (76)	*COPD*- 9.9 (9.4) *Diabetes mellitus*- 18 (22) *Hypertension*- 71 (71) *Previous MI*- 45 (44) *Previous PCI*- 13 (16) *PVD* - 13 (14)	NA	3.1 ± 1 (2.9 ± 0.9)	Intermediary experience of off pump	Hospital stay ICU stay MI Mortality Stroke
Lamy et al. [13] Canada	2377 (2375)	67.5 ± 6.9 (67.6 ± 6.7)	82 (80)	*Diabetes mellitus*– 47.5 (46.5) *Dialysis*– 1.1 (1.7) *Hypertension*– 75.5 (76.2) *Previous MI*– 35.2 (33.8) *Previous PCI*– 9.5 (10) *Previous stroke*– 7.8 (6.7)	NA	3.2 (3.0) ($p < 0.001$)	All had >2 yrs experience and completed >100 procedures	AF MI Mortality New renal failure Stroke
Lamy et al. [14] Canada	2377 (2375)	67.5 ± 6.9 (67.6 ± 6.7)	82 (80)	*Diabetes mellitus*– 47.5 (46.5) *Dialysis*– 1.1 (1.7) *Hypertension*– 75.5 (76.2) *Previous MI*– 35.2 (33.8) *Previous PCI*– 9.5 (10) *Previous stroke*– 7.8 (6.7)	12	3.2 (3.0) ($p < 0.001$)	All had >2 yrs experience and completed >100 procedures	MI Mortality New renal failure Stroke

Table 1: Continued.

Study	No. on (off)	Age years on (off)	Male % on (off)	Comorbidities % on (off)	Length of follow up (mo)	No. of grafts (mean ± SD) on (off)	Experience of surgeons	Outcome measures
Lee et al. [23] Hawaii	30 (30)	66 ± 11.2 (65.5 ± 9.6)	73 (80)	*Diabetes mellitus*– 47.5 (46.5) *Dialysis*– 1.1 (1.7) *Hypertension*– 75.5 (76.2) *Previous MI*– 35.2 (33.8) *Previous PCI*– 9.5 (10) *Previous stroke*– 7.8 (6.7)	N/A	3.6 ± 0.9 (3.1 ± 0.7)	Not mentioned	Hospital stay Mortality Stroke
Lemma et al. [17] Italy	203 (208)	73 (74)	69 (70)	*COPD*– 25.1 (31.7) *Diabetes mellitus* - 43.3 (42.8) *Dialysis*– 13.8 (20.2) *Hypertension*– 82.3 (83.7) *Previous stroke*– 9.9 (9.6) *PVD*– 35 (37.5)	NA	3.3 ± 1 (3.0 ± 1.1)	The surgeons were well qualified, at the plateau of their learning curve, had a well-documented surgical practice, and performed only the procedure they preferred, in which they had expertise and that they used routinely during their daily practice	MI Mortality Renal failure Stroke
Møller et al. [15] Denmark	163 (176)	75.6 ± 4.9 (76.1 ± 5.2)	64 (65)	*COPD*– 8 (11) *Diabetes mellitus*– 18 (18) *Dialysis*– 3.1 (4.5) *Hypertension*– 53 (48) *Previous MI*– 58 (56) *Previous stroke*– 17 (12)	N/A	3.34 ± 0.76 (3.22 ± 0.72) ns	All had >2 yrs experience of off-pump procedures	MI Mortality Stroke

Table 1: Continued.

Study	No. on (off)	Age years on (off)	Male % on (off)	Comorbidities % on (off)	Length of follow up (mo)	No. of grafts (mean ± SD) on (off)	Experience of surgeons	Outcome measures
Møller et al. (2011) Denmark	163 (176)	75.6 ± 4.9 (76.1 ± 5.2)	64 (65)	*COPD*– 8 (11) *Diabetes mellitus*– 18 (18) *Dialysis*– 3.1 (4.5) *Hypertension*– 53 (48) *Previous MI*– 58 (56) *Previous stroke*– 17 (12)	44	3.34 ± 0.76 (3.22 ± 0.72) ns	All had >2 yrs experience of off-pump procedures	MI Mortality Repeat revascularisation Stroke
Muneretto et al. [24] Italy	88 (88)	66 ± 9 (67 ± 8)	59 (63)	*COPD*– 12.5 (11.3) *Diabetes mellitus*– 39.7 (42) *Previous MI*– 40.9 (38.6)	15 ± 12	2.8 ± 0.8 (2.7 ± 0.5) ns	Not mentioned	AF Hospital stay ICU stay MI Mortality Stroke Ventilation time
Nesher et al. [18] Israel	60 (60)	68 ± 5 (67 ± 1)	77 (73)	*Diabetes mellitus*– 21 (20) *Hypertension*– 34 (40)	N/A	2.9 ± 1.5 (2.3 ± 0.9)	Surgeons experienced in both techniques	Hospital stay Stroke Ventilation time
Niranjan et al. [12] UK	*With CSBT*: 20 (20) *Without CSBT*: 20 (20)	*With CSBT*: 66.3 ± 7.3 (67.3 ± 11.2) *Without CSBT*: 66.1 ± 10.8 (67.9 ± 9.5)	*With CSBT*: 80 (75) *Without CSBT*: 80 (95)	*With CSBT*: *Diabetes mellitus*– 20 (10) *dialysis*– 0 (15) *hypertension*– 80 (70) *Without CSBT*: *Diabetes mellitus*– 15 (10) *dialysis*– 5 (5) *hypertension*– 70 (60)	*With CSBT*: N/A *Without CSBT*: N/A	*With CSBT* 3.7 ± 0.7 (3.65 ± 0.7) *Without CSBT* 3.8 ± 0.9 (4.2 ± 0.8)	Not mentioned	AF blood transfusion Hospital stay ICU stay Mortality Stroke Ventilation time

Table 1: Continued.

Study	No. on (off)	Age years on (off)	Male % on (off)	Comorbidities % on (off)	Length of follow up (mo)	No. of grafts (mean ± SD) on (off)	Experience of surgeons	Outcome measures
Rogers et al. CRISP trial [25] UK	53 (53)	75.7 ± 7.7 (76.4 ± 5.8)	76 (78)	*COPD*– 16 (10) *Diabetes mellitus*– 27 (22) *Dialysis*– 0 (0) *Hypertension*– 76 (84) *Previous MI*– 69 (71) *Previous PCI*– 20 (12) *Previous stroke*– 10 (6) *PVD*– 14 (10)	N/A	2–4 grafts per gp but 3–4 grafts performed less frequently in off	Operative experience less in the off-pump group	MI Mortality Renal failure Stroke
Sharma et al. [26] India	288 (293)	72 ± 5.3 (73 ± 5.2)	67.8 (69.2)	*COPD*– 9.8 (10.7) *Diabetes mellitus*– 13.8 (15.1) *Previous MI*– 36.2 (37.6) *Previous PCI*– 21.8 (21.2) *Previous stroke*– 6.6 (9.2) *PVD*– 27.2 (26.6)	12	2.9 (2.7) $P < 0.001$	Not mentioned	MI Mortality New renal–replacement therapy Repeat revascularisation Stroke
Vedin et al. [27] Sweden	37 (33)	65 (65)	84 (78)	*COPD*– 11 (0) *Diabetes mellitus*– 19 (18) *Hypertension*– 46 (52) *Previous MI*– 38 (30)	N/A	3 (3)	Not mentioned	MI Stroke

CSBT: cell saver blood transfusion; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; N/A: nonapplicable; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease.

Table 2: Summary of results.

Parameter	No. of studies	No. of patients off/on	RR [95% CI]	I^2 (%)	P value
Short-term primary outcomes					
Mortality	10	4898/4916	0.83 [0.64, 1.06]	0	0.13
MI	10	4901/4923	0.92 [0.73, 1.15]	10	0.47
New renal failure	8	4418/4436	0.82 [0.61, 1.10]	0	0.18
Stroke	13*	5031/5053	0.8 [0.60, 1.07]	0	0.14
Midterm primary outcomes					
Mortality	6	4217/4231	1.08 [0.87, 1.34]	24	0.47
MI	6	4217/4231	0.85 [0.71, 1.01]	0	0.07
New renal failure	4	3953/3980	0.84 [0.62, 1.15]	0	0.28
Repeat revascularisation	5	4121/4126	1.47 [1.07, 2.01]	0	0.02
Stroke	6	4217/4231	0.87 [0.67, 1.13]	0	0.31
Subgroup analysis of surgeon's experience with respect to repeat revascularisation					
Experienced	3	3730/3731	1.43 [1.01, 2.02]	0	0.04
Not mentioned	2	391/395	1.7 [0.75, 3.83]	0	0.2
Short-term secondary outcomes					
Postoperative AF	5*	2777/2776	0.99 [0.89, 1.09]	0	0.77
Blood transfusions	4	1768/1802	0.9 [0.79, 3.09]	34	0.07
Parameter	No. of studies	MD [95% CI]	Units	I^2 (%)	P value
Ventilation time	3*	−4.57 [-11.23, 2.09]	Hours	97	0.18
ICU stay	3*	−9.87 [-24.52, 4.78]	Hours	97	0.19
Hospital stay	9*	−0.56 [-0.92, −0.36]	Days	79	0.003

*Due to the 2 intervention groups in Niranjan et al. [15] these parameters contain one more intervention group than the number of studies shown. ICU: intensive care unit. AF: atrial fibrillation.

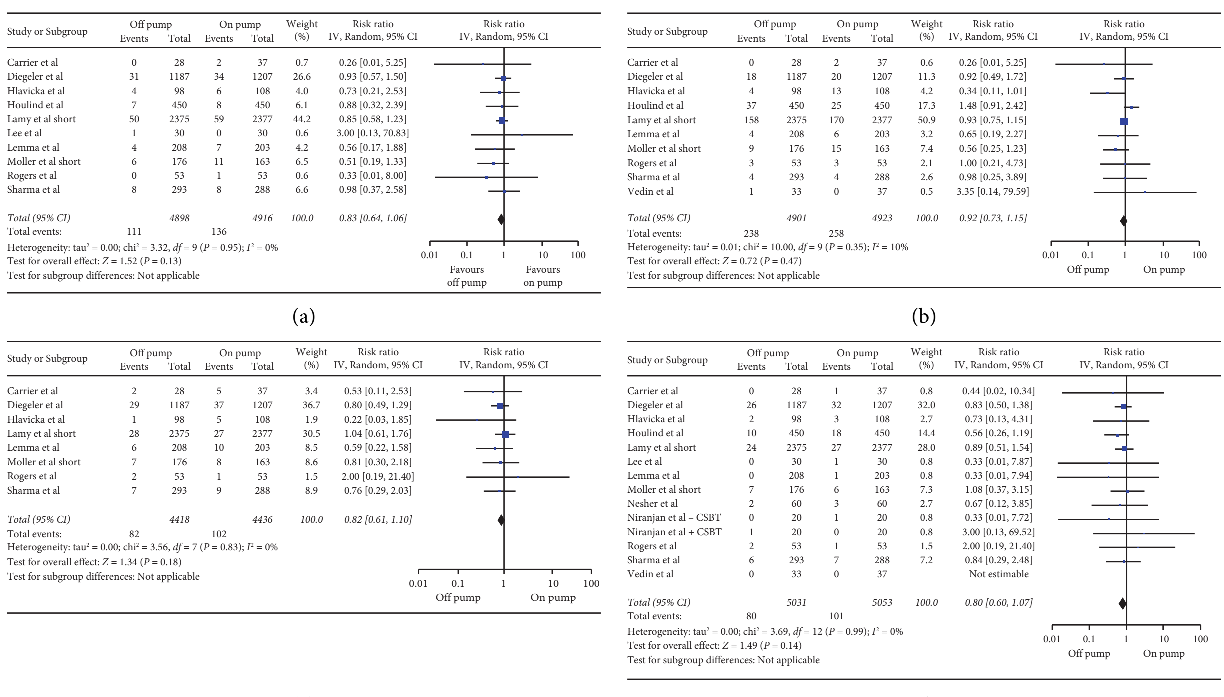

Figure 2: Forest plots of short-term (within 30 days postsurgery) clinical outcomes. Each forest plot contains a table on the left and a graph on the right. The table provides a summary of the data for each study. The graph plots each study's risk ratio (RR) as a box with the 95% confidence intervals indicated by the whiskers. The midvertical line represents an RR of 1 and is essentially a line of no effect. The centre of the black diamond at the bottom of the graph represents the overall RR with the width of the diamond representing the 95% CI. This is in line with the italics writing giving the values for the overall RR with 95% CI. Underneath the table are 2 further rows of statistics including the measurements of heterogeneity and the p value: (a) mortality, (b) myocardial infarction, (c) renal failure, and (d) stroke.

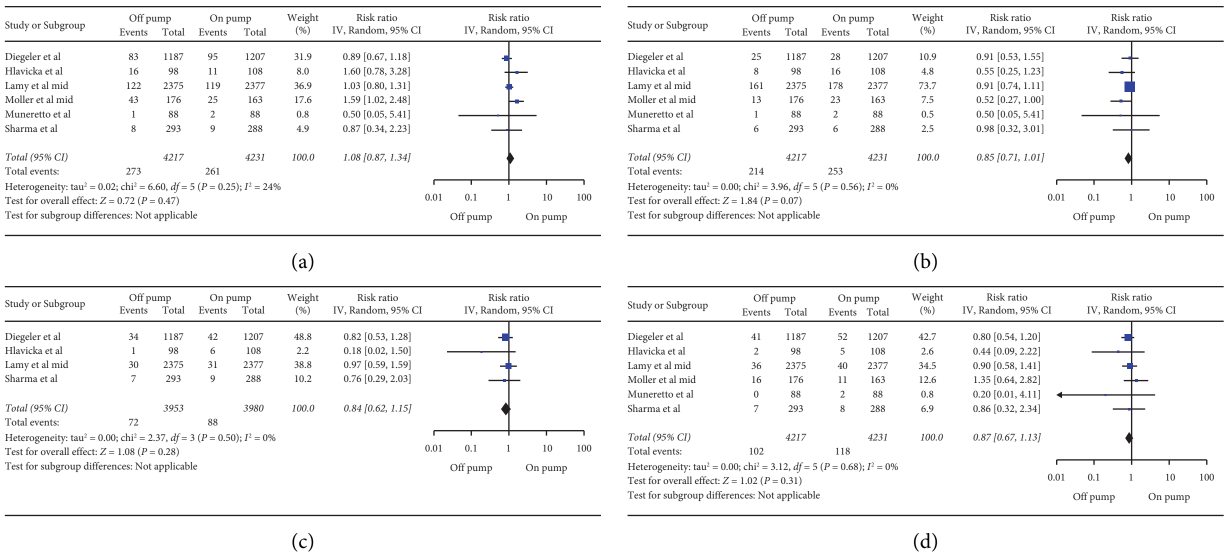

FIGURE 3: Forest plots of midterm (12–44 months) clinical outcomes. (a) mortality, (b) myocardial infarction, (c) renal failure, and (d) stroke. All other details as Figure 1.

3.10. Repeat Revascularisation. Five studies reported the need for repeat revascularisation at midterm follow up. The RR was 1.45 (95% CI 1.04 to 2.02, $I^2 = 0\%$, $p = 0.03$) (Figure 4). A subgroup analysis was also carried out according to whether the surgeons were experienced or this was not mentioned. The RR for the experienced data were 1.43 (95% CI 1.01 to 2.02, $I^2 = 0\%$, $p = 0.04$). The RR for the not mentioned group was 1.7 (95% CI 0.75 to 3.83, $I^2 = 0\%$, $p = 0.20$). The risk of requiring repeat revascularisation was significantly higher in the off-pump group and the experienced group. The funnel plot was asymmetrical (Suppl. file Figure S11).

3.11. Secondary Outcomes at 30 Days: Postoperative Atrial Fibrillation (POAF). Five studies (6 intervention groups) reported the incidence of POAF. The RR for the comparison was 0.99 (95% CI = 0.89 to 1.09; $I^2 = 0\%$; $P = 0.77$) (Suppl. file Figure S12). The risk of having a postoperative atrial fibrillation was not significantly different between the two groups. The funnel plot was asymmetrical (Suppl. file Figure S13).

3.12. Blood Transfusions. Four studies reported whether patients required blood transfusions. The RR for the comparison was 0.90 (95% CI = 0.79 to 1.01; $I^2 = 34\%$; $P = 0.07$) (Suppl. file Figure S14). The risk of needing a blood transfusion postsurgery was not significantly different in the on-pump group compared to the off-pump group. The funnel plot was asymmetrical (Suppl. file Figure S15).

3.13. Ventilation Time. Three studies (4 intervention groups) reported the ventilation time of patients. The MD between the groups was −4.57 hours (95% CI = −11.23 to 2.09; $I^2 = 97\%$; $P = 0.18$) (Suppl. file Figure S16). The difference in ventilation time between the two groups was not significantly different. The funnel plot was asymmetrical (Suppl. file Figure S17).

3.14. ICU Stay. Three studies (4 intervention groups) reported the ICU stay of patients. The MD between the groups was −9.87 hours (95% CI = −24.52 to 4.78; $I^2 = 97\%$; $P = 0.19$) (Suppl. file Figure S18). The difference in ICU stay between the two groups was not significantly different. The funnel plot was asymmetrical (Suppl. file Figure S19).

3.15. Hospital Stay. Nine studies (10 intervention groups) reported the hospital stay of patients. The MD between the groups was −0.56 days (95% CI = −0.92 to −0.19; $I^2 = 79\%$; $P = 0.003$) (Suppl. file Figure S20). The time spent in hospital postoperation was significantly greater in the off-pump group compared to the on-pump group. The funnel plot was asymmetrical (Suppl. file Figure S21).

3.16. Quality of Evidence. All of the included studies were RCTs. In 2 of the included studies, it was unclear if random sequence generation had been used. It was also unclear in most studies whether the allocation had been concealed or not. Surgeons could not be blinded to the type of surgery due to be carried out, so performance bias was not applicable in this case. Approximately equal number of studies used blinding of the outcome assessment. All studies had low risk of bias for attrition and reporting bias. Two studies had other bias. In one case this was due to the sponsor being involved in the study design [17] and in the other due to the troponin I analysis laboratory's involvement in power calculations [18] (Suppl. file Figure S2).

4. Discussion

The aim of this systematic review and meta-analysis was to test the hypothesis that off-pump CABG would have better clinical outcomes compared to on-pump CABG in patients with a mean age ≥65 years. However, the primary outcomes were not significantly different in the short- or midterm. The

Study or Subgroup	Off pump Events	Off pump Total	On pump Events	On pump Total	Weight (%)	Risk ratio IV, Random, 95% CI
1.1.1 Experienced						
Diegeler et al	36	1176	24	1191	38.7	1.52 [0.91, 2.52]
Lamy et al	33	2375	20	2377	33.0	1.65 [0.95, 2.87]
Moller et al	9	176	10	163	13.2	0.83 [0.35, 2.00]
Subtotal (95% CI)		3730		3731	84.8	1.43 [1.01, 2.02]
Total events:	78		54			
Heterogeneity: tau^2 = 0.00; chi^2 = 1.77, *df* = 2 (*P* = 0.41); I^2 = 0%						
Test for overall effect: *Z* = 2.03 (*P* = 0.04)						
1.1.2 Not mentioned						
Hlavicka et al	5	98	3	107	5.1	1.82 [0.45, 7.42]
Sharma et al	10	293	6	288	10.1	1.64 [0.60, 4.45]
Subtotal (95% CI)		391		395	15.2	1.70 [0.75, 3.83]
Total events:	15		9			
Heterogeneity: tau^2 = 0.00; chi^2 = 0.01, *df* = 1 (*P* = 0.90); I^2 = 0%						
Test for overall effect: *Z* = 1.27 (*P* = 0.20)						
Total (95% CI)		*4121*		*4126*	*100.0*	*1.47 [1.07, 2.01]*
Total events:	93		63			
Heterogeneity: tau^2 = 0.00; chi^2 = 1.93, *df* = 4 (*P* = 0.75); I^2 = 0%						
Test for overall effect: *Z* = 2.36 (*P* = 0.02)						
Test for subgroup differences: chi^2 = 0.15, *df* = 1 (*P* = 0.70); I^2 = 0%						

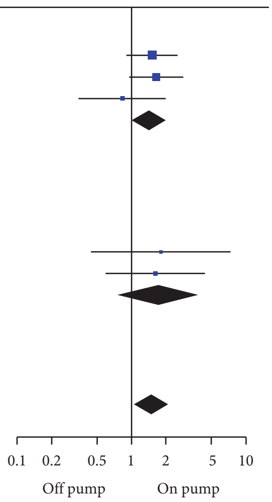

Figure 4: Forest plot of the requirement for revascularisation at midterm follow up. All other details as Figure 1.

only exception was the requirement for repeat revascularisation at midterm follow up, where the risk was significantly lower in the on-pump patients. There were also similarities in the secondary outcomes: ventilation time, ICU stay, requirement for blood transfusion and postoperative atrial fibrillation; whilst the length of hospital stay favoured the off-pump group.

There was a significantly greater need for repeat revascularisation at midterm follow up in the off-pump group. This was only investigated in 5 studies. Nonetheless, possible explanations for this difference could involve 3 factors: the completeness of revascularisation, the surgeon's experience and the number of patients lost to follow up. It has been reported that off-pump surgery is more technically demanding [18], where anastomosing the circumflex artery can be difficult [28]. Although the completeness of revascularisation was rarely mentioned in any of the 14 studies, 4 of the studies with midterm follow up involved the performance of less grafts in the off-pump group [14, 18, 21, 26]. Another related possibility could be the surgeon's experience. In 3 of the studies, the surgeons were experienced [14, 16, 18], whilst this was not mentioned in the other 2 [21, 26]. In order to further investigate this, a subgroup analysis was carried out. The RR was significant for the experienced surgeons and insignificant for the studies, where surgeons' experience was not mentioned. The difference in the numbers of patients involved in each of the subgroups should, however, be noted. This raises the possibly important issue of the number of patients lost to follow up. In the three smaller studies [16, 21, 26], no patients were lost to follow up, whereas Diegeler et al. lost 27 [20] and Lamy et al. lost 1.3% [14]. These losses in the latter 2 studies may reflect the larger numbers of patients in these studies. Regarding the number of MIs in each group it is possible that the number of patients in the on-pump group may have been censored, which may explain the *p* value for this comparison.

The requirement for greater repeat revascularisation can also be compared to other investigations. In a much smaller meta-analysis (only 5 included RCTs) the need for early (within 30 days) repeat revascularisation in the off-pump group was also significantly greater compared to the on-pump group [9]. However, in a mixed-age group longer term meta-analysis (>4 years) repeat revascularisation was similar in the 2 groups [5]. This discussion suggests that further longer-term follow up off-pump vs on-pump CABG involving patients with a mean age ≥65 is needed.

The other significant result was a secondary outcome. According to the charity Age UK, an excess bed day in the NHS costs between £2089 and £2532 per week or approximately £300–360 per day. The MD was −0.56 days (95% CI −0.92 to −0.19). This is <1 day so may not lead to any real cost saving. This would also be in agreement with a long-term RCT, carried out on the >65 s, which showed similar costs for on vs off-pump surgery [29].

4.1. Limitations. There were differences in the cardioplegia solution used in different studies, e.g., blood [15] vs crystalloid [17], which could have been 1 source of the heterogeneity seen in some analyses. Some of the papers are >10–15 years old, and it is possible that surgical techniques have advanced since then. Also, a perennial problem affecting RCTs and meta-analyses investigating on- vs off-pump CABG is whether the studies are sufficiently powered to detect a difference, although this is compensated for by the inclusion of 2 of the largest RCTs completed to date [13, 14, 18].

5. Conclusions

The only primary outcome showing a significant difference was repeat revascularisation. However, there are caveats when considering this difference, despite the significant *p* value. All other primary outcomes including the important ones of risk of dying, MI, and stroke were similar between the two groups. This suggests that in patients with a mean age ≥65 the decision whether to use on or off pump should remain with the operating surgeon [30, 31].

Abbreviations

BP: Blood pressure
CABG: Coronary artery bypass graft
CAD: Coronary artery disease
CENTRAL: Cochrane Central Registry of Controlled Trials
CI: Confidence interval
ICU: Intensive care unit
MD: Mean difference
MI: Myocardial infarction
NICE: National Institute for Health and Care Excellence
PCI: Percutaneous coronary intervention
AF: Atrial fibrillation
PRISMA: Preferred reporting items for systematic reviews and meta-analysis
RCTs: Randomized controlled trials
RR: Risk ratio
Suppl: Supplementary.

Data Availability

All of the data are available in the individual forest and funnel plots.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

NK conceived the project, wrote the original draft, was involved in data analysis, and supervised the team. JT and LE were involved in investigations, data curation, formal analysis, methodology, and software. NS was involved in validation, visualisation, and formal analysis. All authors were involved in reviewing and editing the manuscript. Each author has approved the final version and takes responsibility for their contribution.

Supplementary Materials

Figure S1: search strategy in PubMed. Figure S2: summary of risk of bias table/plot with explanations. In table the colour green represents low risk of bias, the colour orange represents unclear risk of bias and the colour red indicates high risk of bias. One column is blank. This is because surgeons cannot be blinded to the type of surgery they are to perform rendering this analysis nonapplicable. Figure S3: short-term mortality, funnel plot. Figure S4: short-term myocardial infarction, funnel plot. Figure S5: short-term renal failure, funnel plot. Figure S6: short-term stroke, funnel plot. Figure S7: midterm mortality, funnel plot. Figure S8: midterm myocardial infarction, funnel plot. Figure S9: midterm renal failure, funnel plot. Figure S10: midterm stroke, funnel plot. Figure S11: midterm repeat revascularisation, funnel plot. Figure S12: postoperative atrial fibrillation, forest plot. Figure S13: postoperative atrial fibrillation, funnel plot. Figure S14: blood transfusion, forest plot. Figure S15: blood transfusion, funnel plot. Figure S16: ventilation time, forest plot. Figure S17: ventilation time, funnel plot. Figure S18: ICU stay, forest plot. Figure S19: ICU stay, funnel plot. Figure S20: hospital stay, forest plot. Figure S21: hospital stay, funnel plot, Suppl. table 1: Excluded studies with reasons, Suppl. table 2: PRISMA checklist. (*Supplementary Materials*)

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