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Review

On- or off-pump coronary artery bypass grafting for octogenarians: A meta-analysis of comparative studies involving 27,623 patients

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HIGHLIGHTS

- Coronary artery bypass grafting (CABG) is being increasingly offered to octogenarians.
- The issue of superiority of off- or on-pump CABG for octogenarians remains unresolved.
- This largest meta-analysis shows lower in-hospital mortality with off-pump CABG.
- Stroke rate and length of hospital stay are also lower with off-pump CABG.
- Same incidence of other adverse outcomes with off- & on-pump CABG in octogenarians.

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ABSTRACT

Objective: Coronary artery bypass grafting (CABG) is being increasingly offered to octogenarians. Both on- and off-pump CABG are reported as effective surgical revascularization strategies for octogenarians by single institution studies. However, the issue of superiority of one strategy over the other for octogenarians remains unresolved due to limited sample size of these studies. A meta-analysis of studies comparing outcomes of on- and off-pump CABG in octogenarians was undertaken to address the issue.
Methods: A literature search was conducted from 1966 through September 2016 using MEDLINE, EMBASE, Scopus and Web of Science to identify relevant articles. Primary outcomes of interest included in-hospital mortality and stroke. Secondary outcomes of interest were atrial fibrillation, acute renal failure, reoperation for bleeding, deep sternal wound infection, myocardial infarction, intensive therapy unit (ITU) stay and hospital stay. The random effects model was used to calculate the outcomes of both binary and continuous data to control any heterogeneity between the studies. Heterogeneity amongst the trials was determined by means of the Cochran Q value and quantified using the I^2 inconsistency test. All p-values were 2-sided and a 5% level was considered significant.
Results: Sixteen retrospective studies (18,685 on-pump patients and 8938 off-pump patients) were included in the systematic review. In-hospital mortality (pooled OR = 0.64, 95% CI = 0.44 to 0.93; p = 0.02), stroke rate (pooled OR = 0.61, 95% CI = 0.48 to 0.76; p < 0.001) and length of hospital stay (pooled WMD = +0.29, 95% CI = +0.02 to +0.56; p = 0.04) were significantly lower in the off-pump patients. Atrial fibrillation (p = 0.36), acute renal failure (p = 0.47), reoperation for bleeding (p = 0.99), deep sternal wound infection (p = 0.59), myocardial infarction (p = 0.93), and length of ITU stay (p = 0.27) were comparable.
Conclusion: Off-pump compared to on-pump CABG offers surgical myocardial revascularization to octogenarians with lower in-hospital mortality, stroke rate and length of hospital stay with similar incidence of other adverse outcomes. Preferentially offering off-pump CABG to octogenarians could translate into reduced economic burden on the healthcare providers.

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1. Introduction

An increasing number of octogenarian patients are being referred for coronary artery bypass grafting (CABG) [1]. Octogenarians are deemed high-risk due to the presence of significant co-morbidities and CABG in this group of patients is associated with increased risk of death and overall postoperative morbidity. This results in prolonged length of hospital stay with increasing economic burden. Off-pump CABG is a well-established strategy for surgical myocardial revascularization that has been extensively scrutinised over the past two decades [2]. It is regarded as the preferred strategy for CABG in high-risk patients [3]. Both on- and off-pump CABG are reported as effective surgical revascularization strategies for octogenarians by single institution studies [4,5]. However, the issue of superiority of one strategy over the other for octogenarians remains unresolved due to limited sample size of these studies. We performed a meta-analysis of the published studies comparing outcomes of on- and off-pump CABG in octogenarians to address the issue.

2. Methods

2.1. Literature search

A systematic search was conducted on 3rd October 2016 by applying the following two search strategies in the US National Library of Medicine – National Institutes of Health PubMed search engine:

1. (Off Pump [Title] OR OPCAB[Title] OR beating heart[Title])
2. (Octogenarians [Title] OR aged, 80 and over [Title] OR 80 years [Title])

English scientific literature was reviewed primarily from 1966 through September 2016. The resulting titles and abstracts were screened for relevance, followed by evaluation of the selected publications in their entirety.

Additionally, EMBASE, Scopus and Web of Science databases were also searched. A manual search was also performed for publications in keeping with the above criteria. The publication selection process is illustrated in Fig. 1.

Search strategies #1 and #2 described above yielded 173 and 241 results respectively. Of the 173 results from search strategy #1, 163 were excluded on screening, two were excluded due to lack of parameters of interest and one was excluded due to overlapping cohort, leaving 7 publications for analysis. Of the 241 results from search strategy #2, 225 were excluded on screening. On further evaluation, 7 publications were excluded due to lack of parameters of interest and two was excluded due to overlapping cohort leaving 6 publications for analysis.

A further manual search was conducted which yielded 11 studies. Eight of these were duplicate studies as they were common to the search strategies #1 and #2 so these were excluded. The remaining 3 studies were added to the above 13 studies yielding a grand total of sixteen studies for our final analysis. All studies were retrospective, non-randomised and observational. Publication dates ranged from 2000 to 2013.

2.2. Data extraction

Data were extracted by two reviewers (HK and MU) and in the case of discrepancy the decision was taken by consensus. The following information was extracted from each study: first author, year of publication, study population characteristics, study design (prospective, retrospective or other), inclusion and exclusion criteria, number of patients operated on with each technique, quality of study and postoperative outcome measures discussed below (Table 1).

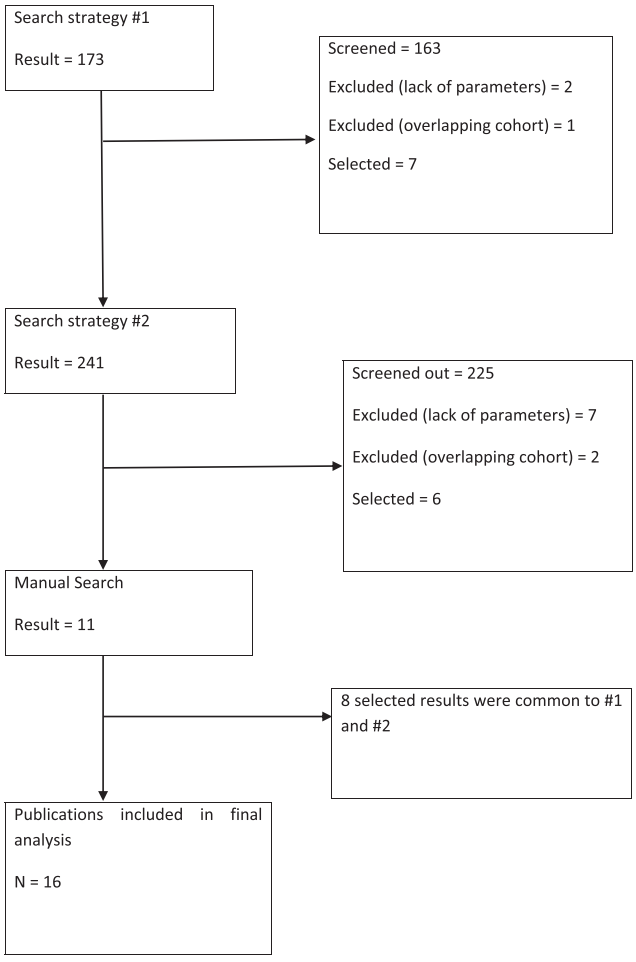

Fig. 1. Flow chart depicting study selection for meta-analysis.

The meta-analysis was performed in line with the recommendations of the proposal for reporting meta-analysis of observational studies in epidemiology [6]. The quality of the non-randomised studies was assessed by using a modified Newcastle–Ottawa Scale [7]. The quality of the studies was evaluated by examining three items: patient selection, comparability of on-pump and off-pump groups and assessment of outcomes.

2.3. Inclusion criteria

The following criteria were used to include studies in our analysis: studies comparing off-pump versus on-pump CABG in octogenarian patients; where several articles reported on the same patient cohort, we selected the most recent article or the article with the greatest detail of information.

2.4. Exclusion criteria

The following criteria were used to exclude studies from our analysis: studies in which the surgical technique (whether off-pump or on-pump) could not be defined; studies in which the outcome of comparison of both techniques was not reported or it was not possible to calculate this from the published results; and studies that contained a zero for the outcome of interest in two cells of the cross-tabulation tables for both off-pump or on-pump

Table 1
Characteristics of studies included in the meta-analysis.

Author	Year of publication	Study population characteristics	Study design	Inclusion & exclusion criteria	Number of patients		NOS	Outcomes
					OPCAB	CPB		
Ricci [8]	2000	≥80 years	Retrospective	Only octogenarians, Conversions included in CPB group, isolated CABG	97	127	7	Early mortality, stroke, DSWI, ARF, MI, RF
Yokoyama [9]	2000	≥80 years	Retrospective	High-risk patients, isolated CABG	28	58	7	Early mortality, neurologic complication (stroke, TIA, or prolonged mental status changes), ARF, prolonged ventilator dependence beyond 3 days, postoperative bleeding requiring reexploration, ITU stay & hospital stay
Demaria [10]	2002	≥80 years	Retrospective	Only octogenarians, isolated CABG	62	63	7	Early mortality, stroke, RF
Hoff [11]	2002	≥80 years	Retrospective	Only octogenarians, Emergency & MIDCAB operations excluded	60	169	7	Early mortality, stroke, DSWI, ARF, MI, RF, AF, ventilated > 48 h, hospital costs
Shimokawa [12]	2003	≥80 years	Retrospective	Only octogenarians, isolated CABG	25	18	7	Early mortality, stroke, blood transfusion, DSWI, ARF, RF, AF, ventilated > 48 h, ITU stay, hospital stay
Lin [13]	2003	≥80 years	Retrospective	Only octogenarians, isolated CABG	17	12	7	Early mortality, stroke, blood transfusion, re-exploration for bleeding, ARF, MI, RF, AF, ventilated > 48 h, ITU stay, hospital stay
D'Alfonso [14]	2004	≥80 years	Retrospective	Only octogenarians, isolated CABG	73	41	7	Early mortality, stroke, MI, late mortality
Nagpal [15]	2006	≥80 years	Retrospective	Only octogenarians, isolated CABG	131	105	7	Early mortality, stroke, blood transfusion, re-exploration for bleeding, ARF, MI, RF, AF, ventilated > 48 h, ITU stay, hospital stay
Tugtekin [16]	2007	≥80 years	Retrospective	Only octogenarians, isolated CABG	107	237	7	Early mortality, stroke, blood transfusion, re-exploration for bleeding, ARF, MI, RF, AF, ventilated > 48 h, ITU stay, hospital stay
Serrão [17]	2010	≥80 years	Retrospective	Only octogenarians, isolated CABG	65	36	7	Early mortality, stroke, blood transfusion, re-exploration for bleeding, ARF, MI, RF, AF, ventilated > 48 h, ITU stay, hospital stay, late survival
Saleh [18]	2011	≥80 years	Retrospective, PMA	Only octogenarians, isolated CABG	156	187	8	Early mortality, stroke, blood transfusion, re-exploration for bleeding, use of inotropes, ARF, MI, RF, AF, ventilated > 48 h, ITU stay, hospital stay
LaPar [19]	2011	≥80 years	Retrospective	Only octogenarians, isolated CABG	404	1589	7	Early mortality, stroke, blood transfusion, re-exploration for bleeding, ARF, MI, RF, AF, ventilated > 48 h, ITU stay, hospital stay
Sarin [20]	2011	≥80 years	Retrospective, PMA	Only octogenarians, isolated CABG	540	397	8	Early mortality, stroke, blood transfusion, re-exploration for bleeding, ARF, MI, RF, AF, ventilated > 48 h, ITU stay, hospital stay, late survival
Vasques [21]	2013	≥80 years	Retrospective, PMA	Only octogenarians, isolated CABG	91	94	8	Early mortality, stroke, LCOS, ARF, re-exploration for bleeding, ITU stay
Raja [22]	2013	≥80 years	Retrospective, PMA	Only octogenarians, isolated CABG	217	73	8	Early mortality, stroke, blood transfusion, re-exploration for bleeding, ARF, MI, RF, AF, ventilated > 48 h, ITU stay, hospital stay
Cavallaro [23]	2014	≥80 years	Retrospective, PMA		6865	15479	8	Early mortality, stroke, mediastinitis, hospital cots, ARF, RF, hospital stay

AF = atrial fibrillation; ARF = acute renal failure; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; ITU = intensive therapy unit; LCOS = low cardiac output syndrome; MI = myocardial infarction; NOS = Newcastle-Ottawa score; OPCAB = off-pump coronary artery bypass; PMA = propensity matched analysis; RF = renal failure.

groups. In addition, all non-English studies, animal studies as well as review articles, case reports and editorials were excluded.

2.5. Outcomes of interest

Primary outcomes of interest included in-hospital mortality and stroke. Secondary outcomes of interest were atrial fibrillation, acute renal failure, reoperation for bleeding, deep sternal wound infection, myocardial infarction, ITU stay and hospital stay.

2.6. Statistical analysis

Data from the individual eligible studies were entered into a spreadsheet for further analysis. StatsDirect 2.5.7 (StatsDirect, Altrincham, UK) was used to perform the statistical analysis. Weighted mean differences (WMD) were calculated for the effect size of continuous variables such as hospital stay and ITU stay. Pooled odds ratios (OR) were calculated for discrete variables such as stroke and in-hospital mortality rates.

The random effects model (DerSimion Laird) was used to calculate the outcomes of both binary and continuous data to control any heterogeneity between the studies. Heterogeneity amongst the trials was determined by means of the Cochran Q value and quantified using the I^2 inconsistency test. In this study, we did not perform meta-regression or sensitivity analysis because of the small number of studies included. All p-values were 2-sided and a 5% level was considered significant.

3. Results

The included16 studies [8–23] compared a total of 18,685 patients in the on-pump group to 8938 in the off-pump group (Table 1). For the purpose of this meta-analysis from this cohort, we selected 10,548 patients in the on-pump group that had been propensity-matched to 8722 patients in the off-pump group. All the included studies had a Newcastle-Ottawa scale assessment score of 7 or greater. Table 2 summarises the results from the meta-analysis.

Table 2
Summary of findings of the meta-analysis.

	Included Studies	OPCABG (N)	ONCABG (N)	Weighted Mean Difference (95% CI)	Pooled Odds Ratio (95% CI)	Heterogeneity Cochrane Q, I^2 (95% CI)	Publication Bias (92.5% CI)
Primary Outcome							
In-hospital mortality	14	8439	10401	–	0.64 (0.44–0.93)	26.3, 50.5% (0–72%)	0.38 (−3.07 to 3.83)
Stroke	16	8722	10,548	–	0.61 (0.48–0.76)	13.3, 0% (0–46%)	−1.07 (−1.79 to −0.35)
Secondary outcomes							
Atrial fibrillation	10	1613	2837	–	0.85 (0.60–1.21)	31.5, 71.5% (35–84%)	1.81 (−0.34 to 3.96)
Acute renal failure	9	8125	9590	–	0.95 (0.83–1.09)	8.5, 5.8% (0–57%)	−0.83 (−1.54 to −0.12)
Reoperation for bleeding	11	1469	1762	–	1.00 (0.67–1.47)	7.17, 0% (0–53%)	−0.36 (−2.16 to 1.44)
Deep sternal wound infections	7	7511	7820	–	1.34 (0.47–3.82)	5.36, 25.3% (0–72%)	−0.31 (−1.09 to 0.47)
Myocardial infarction	8	1442	2552	–	1.03 (0.54–1.99)	8.51, 29.5% (0–69%)	−0.81 (−4.61 to 2.99)
ITU stay	8	2138	2556	−0.33 (−0.92 to 0.26)	–	29.2, 76% (42.8–86%)	−0.45 (−5.61 to 4.70)
Hospital Stay	8	7841	9.036	+0.29 (0.02–0.56)	–	4.44, 0% (0–56%)	−0.47 (−1.42 to 0.47)

CI = confidence interval; ITU = intensive therapy unit; ONCABG = on-pump coronary artery bypass grafting; OPCABG = off-pump coronary artery bypass grafting.

3.1. Primary outcomes

3.1.1. In-hospital mortality

Fourteen studies assessed the in-hospital mortality. There was statistical heterogeneity between studies (Cochran Q = 26.3, p = 0.02; I^2 = 50.5%, 95% CI = 0%–72%). There was no publication bias between the studies (Horbold-Egger: bias = 0.38, 92.5% CI = −3.07 to 3.83, p = 0.82). In the random effects model, there was significant lower mortality rate in the off-pump compared to on-pump group (Pooled OR = 0.64, 95% CI = 0.44 to 0.93; p = 0.02) (Fig. 2).

3.1.2. Stroke

Sixteen studies assessed the rate of stroke. There was no statistical heterogeneity between studies (Cochran Q = 13.3.3, p = 0.10; I^2 = 0%, 95% CI = 0%–46%). There was significant publication bias between the studies (Horbold-Egger: bias = −1.07, 92.5% CI = −1.79 to −0.35, p = 0.01). In the random effects model, there was significant lower stroke rate in the off-pump compared to on-pump groups (Pooled OR = 0.61, 95% CI = 0.48 to 0.76; p < 0.001) (Fig. 3).

3.2. Secondary outcomes

3.2.1. Atrial fibrillation

Ten studies assessed the rate of atrial fibrillation. There was significant statistical heterogeneity between studies (Cochran Q = 31.5, p = 0.0002; I^2 = 71.5%, 95% CI = 35%–84%). There was no publication bias between the studies (Horbold-Egger: bias = 1.81, 92.5% CI = −0.34 to 3.96, p = 0.12). In the random effects model,

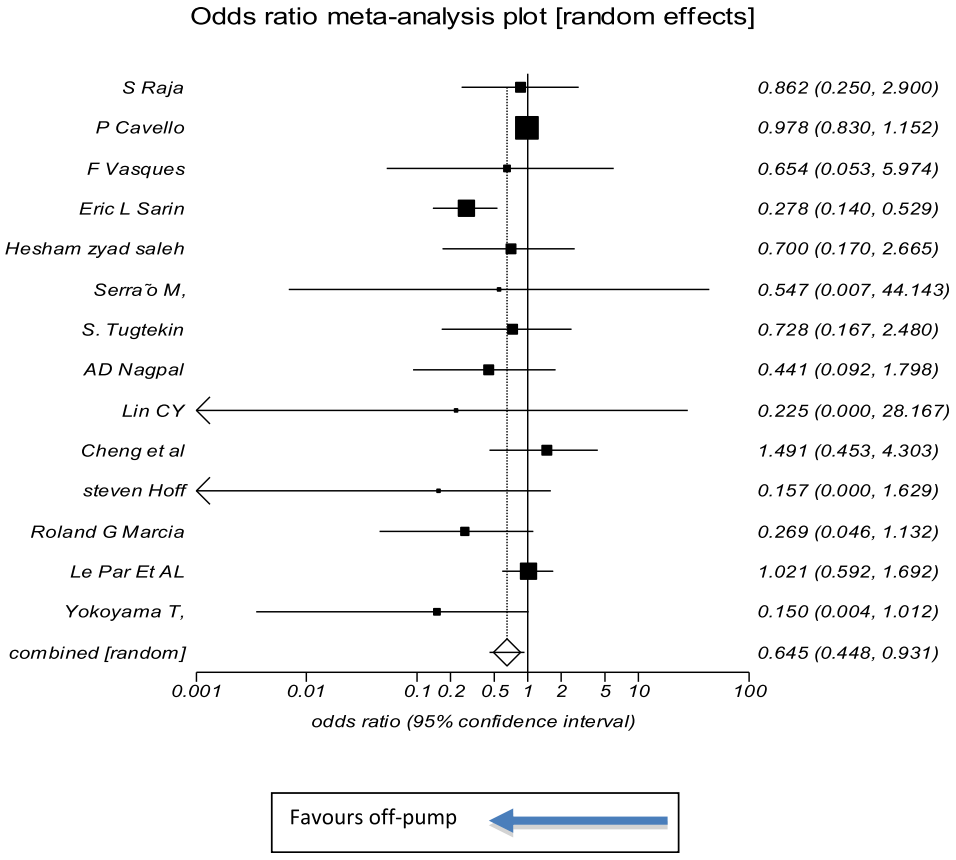

Fig. 2. Forest plot of pooled result for in-hospital mortality.

there was no significant difference in the rate of atrial fibrillation in the off-pump compared to on-pump groups (Pooled OR = 0.85, 95% CI = 0.60 to 1.21; p = 0.36) (Fig. 4).

3.2.2. Acute renal failure

Nine trials reported on the rate of renal failure between the two groups. There was no significant statistical heterogeneity between the nine studies (Cochran Q = 8.50, p = 0.39; I^2 = 5.8%, 95% CI = 0%–57%). There was significant publication bias between the studies (Horbold-Egger: bias = −0.83, 92.5% CI = −1.54 to −0.12, p = 0.04) In the random effects model, there was no significant difference in the rate of acute renal failure between the off-pump and on-pump groups (Pooled OR = 0.95, 95% CI = 0.83 to 1.09; p = 0.47) (Fig. 5).

3.2.3. Reoperation for bleeding

Eleven trials reported on the rate of reoperations for bleeding between the two groups. There was no significant statistical heterogeneity between the eleven studies (Cochran Q = 7.17, p = 0.62; I^2 = 0%, 95% CI = 0%–53%). There was no publication bias between the studies (Horbold-Egger: bias = −0.36, 92.5% CI = −2.16 to 1.44, p = 0.69). In the random effects model, there was no significant difference in the reoperation for bleeding rates between the off-pump and on-pump groups (Pooled OR = 1.00, 95% CI = 0.67 to 1.47; p = 0.99) (Fig. 6).

3.2.4. Deep sternal wound infection

Seven trials reported on the rate of deep sternal wound infection between the two groups. There was no significant statistical heterogeneity between the seven studies (Cochran Q = 5.36, p = 0.25; I^2 = 25.3%, 95% CI = 0%–72%). There was no publication bias between the studies (Horbold-Egger: bias = −0.31, 92.5% CI = −1.09 to 0.47, p = 0.42). In the random effects model, there was no significant difference in the deep sternal infection rates between the off pump and on-pump groups (Pooled OR = 1.34, 95% CI = 0.47 to 3.82; p = 0.59) (Fig. 7).

3.2.5. Myocardial infarction

Eight trials reported on the rate of myocardial infarction between the two groups. There was no significant statistical heterogeneity between the eight studies (Cochran Q = 8.51, p = 0.20; I^2 = 29.5%, 95% CI = 0%–69%). There was no publication bias between the studies (Horbold-Egger: bias = −0.81, 92.5% CI = −4.61 to 2.99, p = 0.65). In the random effects model, there was no significant difference in the myocardial infarction rates between the off-pump and on-pump groups (Pooled OR = 1.03, 95% CI = 0.54 to 1.99; p = 0.93) (Fig. 8).

3.2.6. ITU stay

Eight trials reported on the ITU stay between the two groups. There was significant statistical heterogeneity between the eight studies (Cochran Q = 29.2, p = 0.0001; I^2 = 76%, 95% CI = 42.8%–86%). There was no publication bias between the studies (Egger:

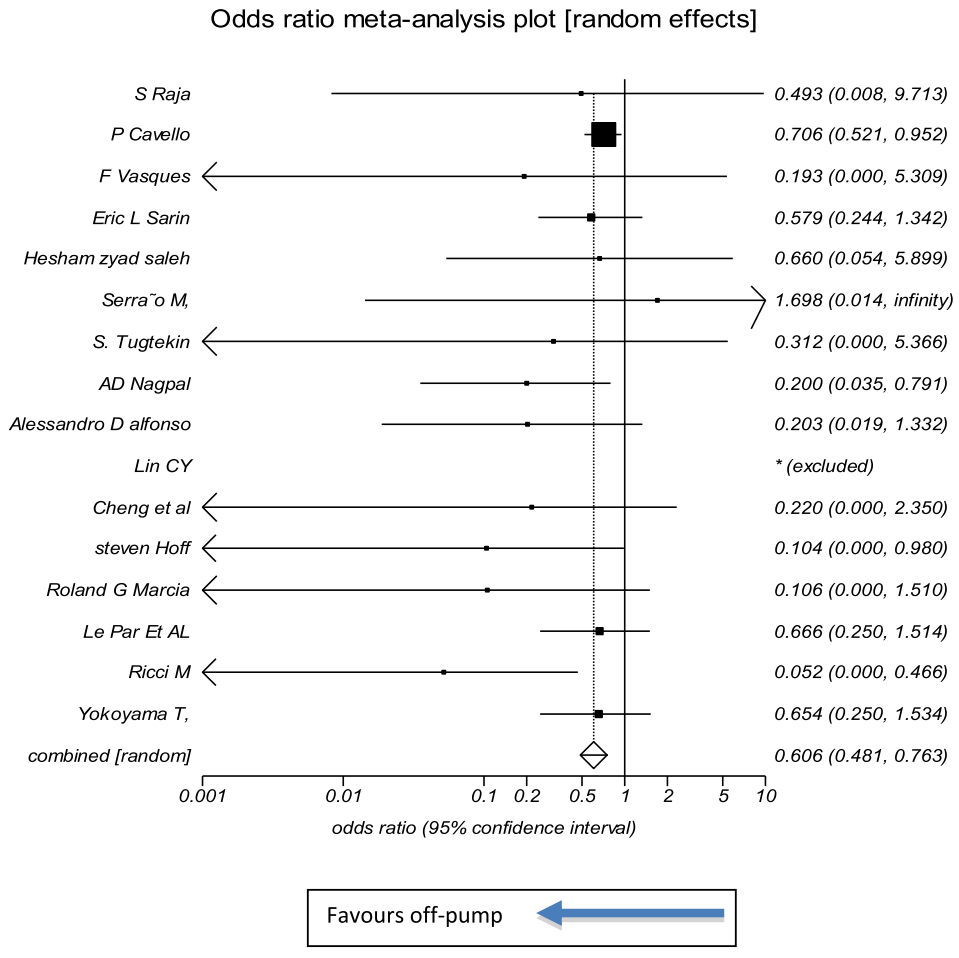

Fig. 3. Forest plot of pooled result for stroke.

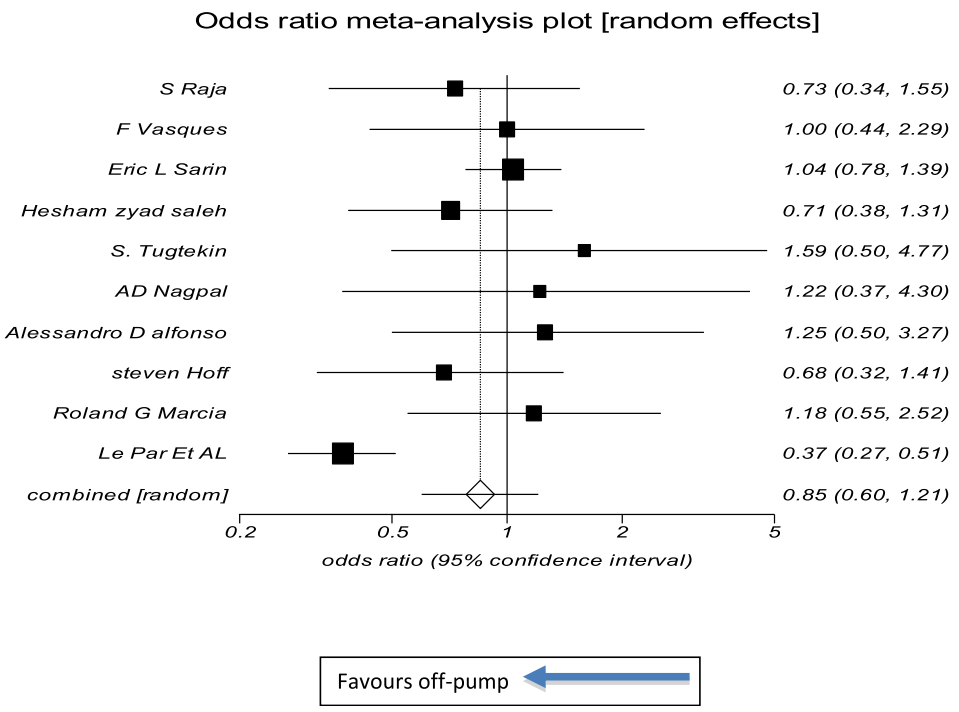

Fig. 4. Forest plot of pooled result for atrial fibrillation.

bias = −0.45, 92.5% CI = −5.61 to 4.70, p = 0.83). In the random effects model, there was no significant difference in the ITU stay between the off-pump and on-pump groups (pooled WMD = −0.33, 95% CI = −0.92 to +0.26; p = 0.27) (Fig. 9).

3.2.7. Hospital stay

Eight trials reported on the hospital stay between the two groups. There was no significant statistical heterogeneity between the eight studies (Cochran Q = 4.44, p = 0.72; I^2 = 0%, 95% CI = 0%–

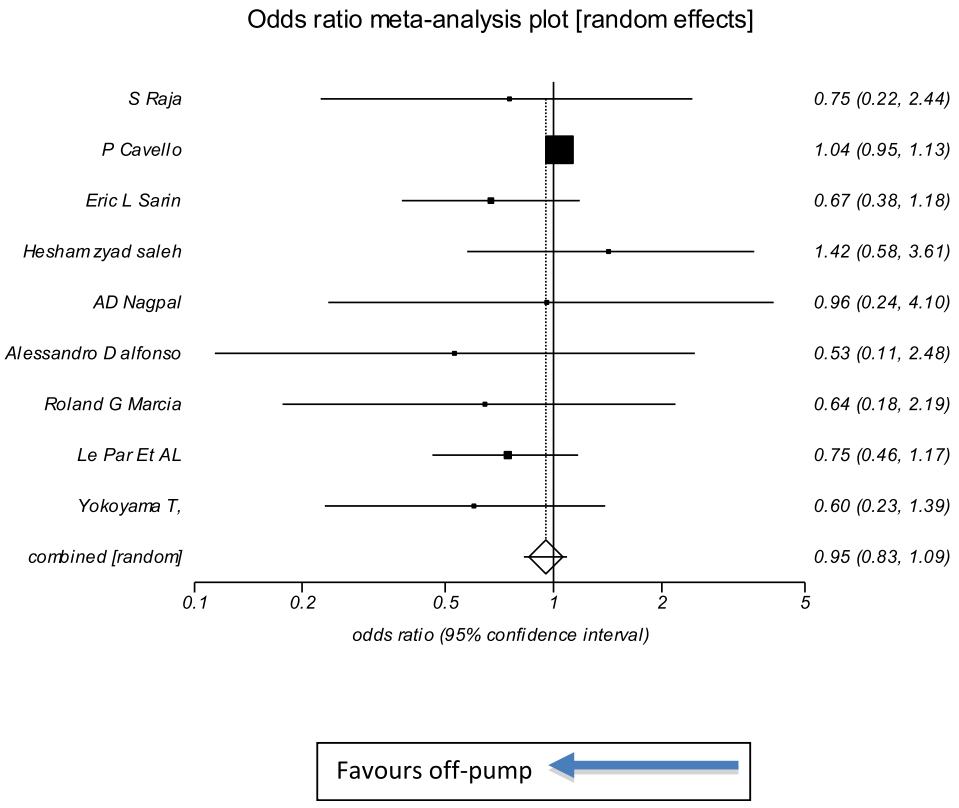

Fig. 5. Forest plot of pooled result for acute renal failure.

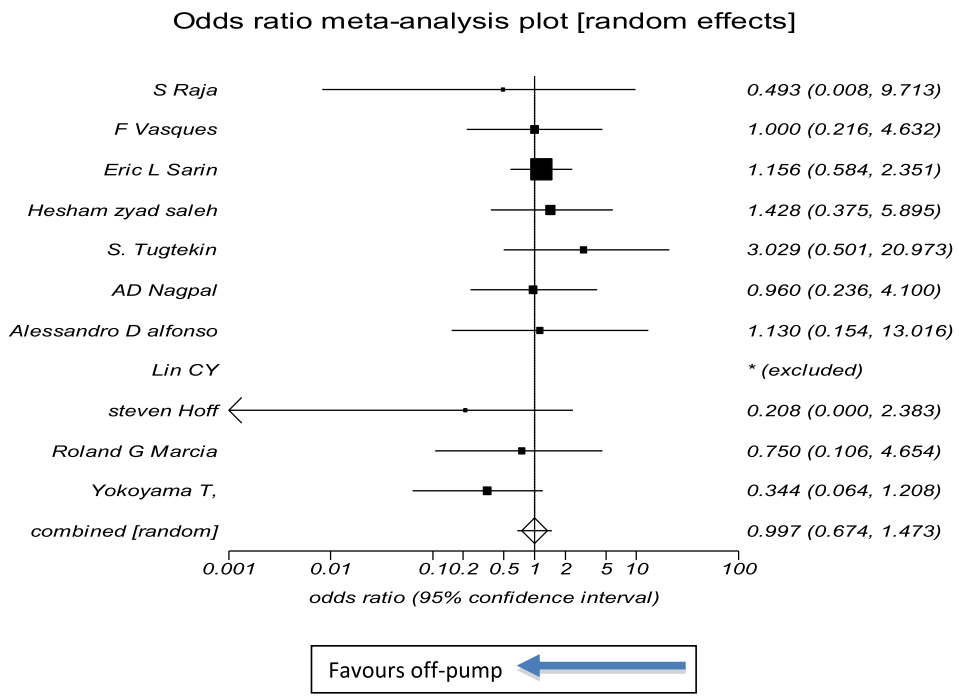

Fig. 6. Forest plot of pooled result for reoperation for bleeding.

56%). There was no publication bias between the studies (Egger: bias = −0.47, 92.5% CI = −1.42 to 0.47, p = 0.27) In the random effect model, there was a significantly lower hospital stay in the off-pump compared to the on-pump group (pooled WMD = +0.29, 95% CI = +0.02 to +0.56; p = 0.04) (Fig. 10).

4. Discussion

Our pooled analysis demonstrates that octogenarians undergoing off-pump CABG experience lower in-hospital mortality, lower stroke rates and shorter hospital stay. All other adverse events are comparable for octogenarians undergoing on-pump and off-pump CABG.

The reported mortality rates in literature for octogenarians are higher than those observed for younger groups. Studies show that the 30-day mortality and the incidence of postoperative complications increase significantly with age. In the analysis of 6057 patients who underwent isolated CABG between 1996 and 2002, the 30-day mortality rate and the incidence of postoperative complications were found to largely escalate with age [24].

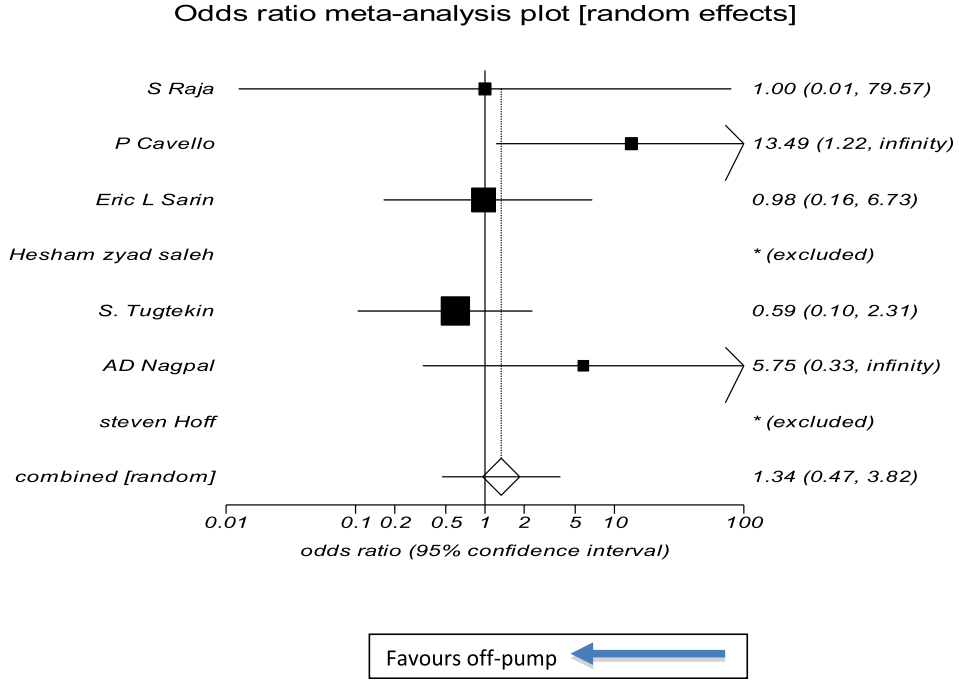

Fig. 7. Forest plot of pooled result for deep sternal wound infection.

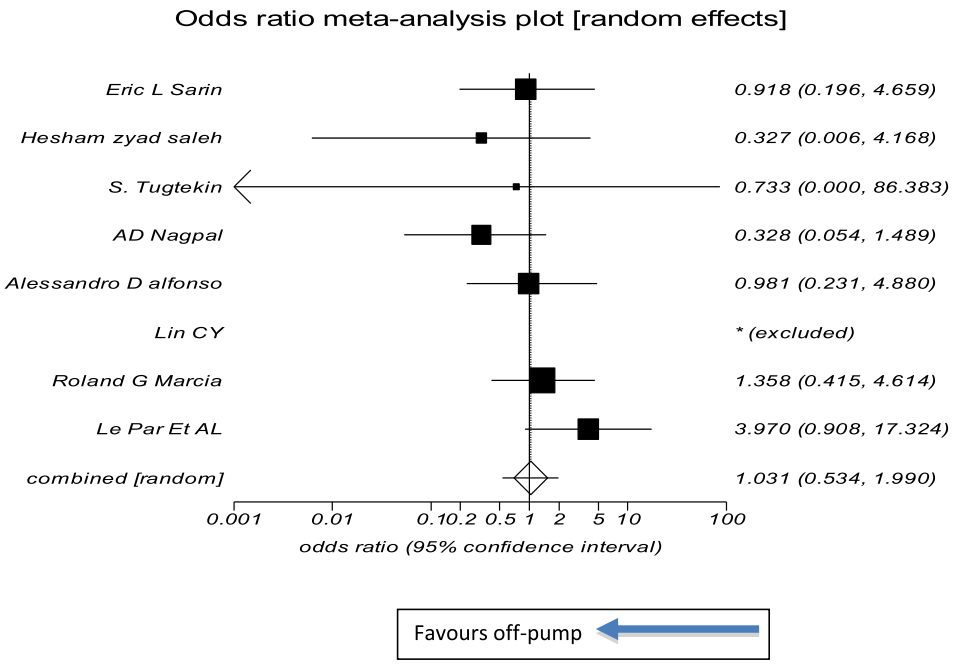

Fig. 8. Forest plot of pooled result for myocardial infarction.

Simultaneously, the costs of hospitalization in older patients who undergo CABG are greater. The observed differences are mostly accounted for by the extended hospital stay and higher incidence of postoperative complications [25,26].

Complete off-pump myocardial revascularization in the hands of highly trained teams appear to be associated with comparable in-hospital mortality, a reduced risk of early morbidity particularly stroke as well as shorter hospital stay [27]. Our meta-analysis validates this concept for the octogenarian population. The most plausible explanation for a difference in in-hospital mortality could be that on-pump CABG was preferentially offered to patients undergoing emergency surgery that affects in-hospital survival. The difference in stroke could be explained mainly by the avoidance of cross clamping and aortic cannulation in off-pump CABG as none of the studies included in the meta-analysis mentioned "no touch" techniques. The shorter length of hospital stay for off-pump CABG patients could be partly attributed to lower stroke rate as postoperative stroke with neurological disability requires protracted

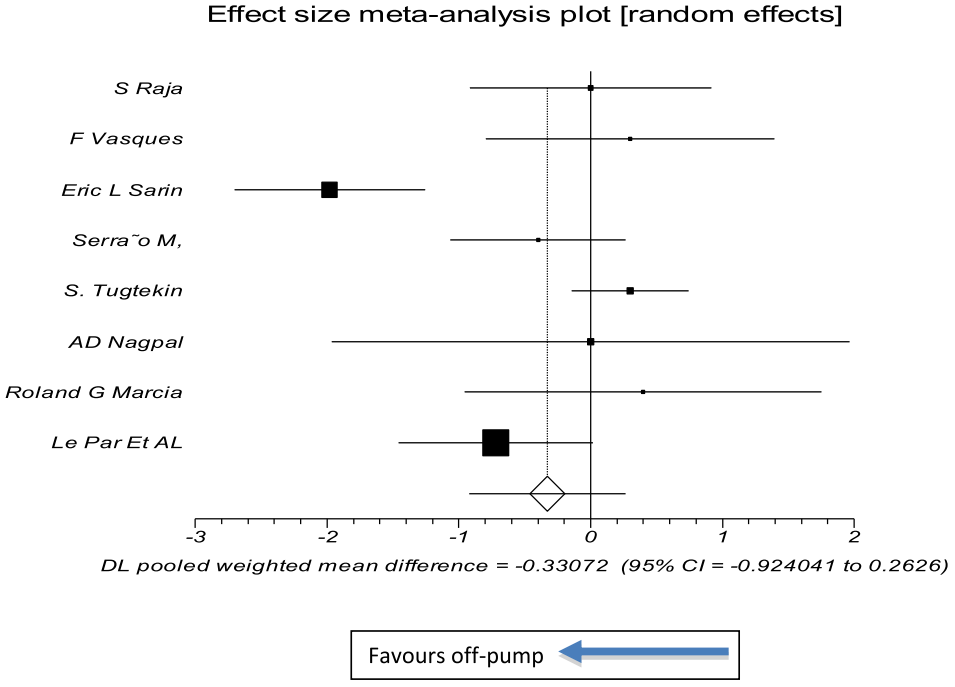

Fig. 9. Forest plot of pooled result for length of ITU stay.

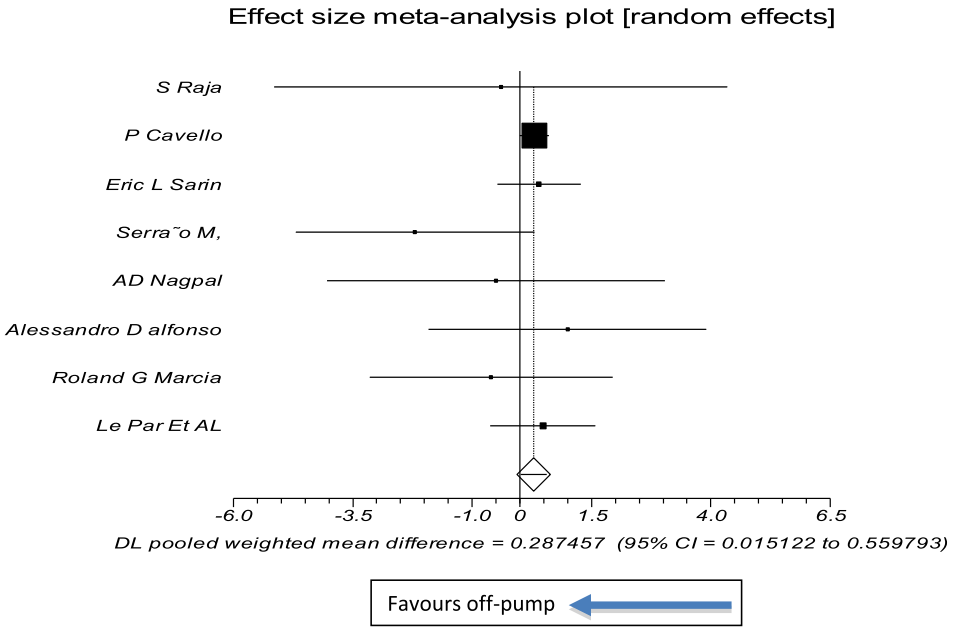

Fig. 10. Forest plot of pooled result for length of hospital stay.

institutional care that translates into increased length of hospital stay and significant economic burden.

There are several caveats to the interpretation of the results of this meta-analysis, primarily arising out of the observational design and retrospective data collection in the included studies. Because the decision to treat patients using either modality was at the discretion of treating physicians, selection bias was inevitable. This may have resulted in systematic differences in variables, which could have influenced outcomes with either treatment modality. However, this pooled analysis of 27,623 patients is the largest meta-analysis to date on the subject. It has almost 9500 patients more than the previously published meta-analysis by Altarabsheh et al. [28]. It is a well-recognised fact that the ability to detect statistical significance increases with increasing sample size, especially when the event rates are low. The purists would argue that a randomised controlled trial would be the best tool to resolve the issue of superiority of off-pump or on-pump CABG in octogenarians. However, conducting a trial with a considerable sample size would have major implications both financially as well as effort-wise.

5. Conclusion

Off-pump compared to on-pump CABG offers surgical myocardial revascularization to octogenarians with lower in-hospital mortality, stroke rate and length of hospital stay with similar incidence of other adverse outcomes. Preferentially offering off-pump CABG to octogenarians could translate into reduced economic burden on the healthcare providers.

Ethical approval

Not required.

Sources of funding

None.

Author contribution

Study design. Shahzad Raja.
Data collection. Salman Butt. Umberto Benedetto.
Data Analysis. Mohsin Uzzaman.
Writing. Habib Khan/Shahzad Raja.

Conflicts of interest

None.

Trial registry number

Researchregistry2452.

Guarantor

Habib Khan.

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