

Off-pump versus on-pump coronary artery bypass surgery: meta-analysis and meta-regression of 13,524 patients from randomized trials

Cirurgia de revascularização miocárdica com CEC versus sem CEC: meta-análise e meta-regressão de 13.524 pacientes de estudos randomizados

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Abstract

Background: Most recent published meta-analysis of randomized controlled trials (RCTs) showed that off-pump coronary artery bypass graft surgery (CABG) reduces incidence of stroke by 30% compared with on-pump CABG, but showed no difference in other outcomes. New RCTs were published, indicating need of new meta-analysis to investigate pooled results adding these further studies.

Methods: MEDLINE, EMBASE, CENTRAL/CCTR, SciELO, LILACS, Google Scholar and reference lists of relevant articles were searched for RCTs that compared outcomes (30-day mortality for all-cause, myocardial

infarction or stroke) between off-pump versus on-pump CABG until May 2012. The principal summary measures were relative risk (RR) with 95% Confidence Interval (CI) and *P* values (considered statistically significant when <0.05). The RR's were combined across studies using DerSimonian-Laird random effects weighted model. Meta-analysis and meta-regression were completed using the software Comprehensive Meta-Analysis version 2 (Biostat Inc., Englewood, New Jersey, USA).

Results: Forty-seven RCTs were identified and included 13,524 patients (6,758 for off-pump and 6,766 for on-pump CABG). There was no significant difference between off-

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Abbreviations, Acronyms & Symbols

CABG	Coronary artery bypass graft surgery
CENTRAL/CCTR	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
LILACS	Literatura Latino-Americana e do Caribe em Ciências da Saúde
MeSH	Medical Subject Heading
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
RR	Risk Ratio
SciELO	Scientific Electronic Library Online

pump and on-pump CABG groups in RR for 30-day mortality or myocardial infarction, but there was difference about stroke in favor to off-pump CABG (RR 0.793, 95% CI 0.660-0.920, $P=0.049$). It was observed no important heterogeneity of effects about any outcome, but it was observed publication bias about outcome "stroke". Meta-regression did not demonstrate influence of female gender, number of grafts or age in outcomes.

Conclusion: Off-pump CABG reduces the incidence of post-operative stroke by 20.7% and has no substantial effect on mortality or myocardial infarction in comparison to on-pump CABG. Patient gender, number of grafts performed and age do not seem to explain the effect of off-pump CABG on mortality, myocardial infarction or stroke, respectively.

Descriptors: Meta-Analysis. Coronary artery bypass, off-pump. Cardiopulmonary bypass.

Resumo

Introdução: A meta-análise mais recente de estudos randomizados controlados (ERC) mostrou que cirurgia de revascularização (CRM) sem circulação extracorpórea (CEC) reduz a incidência de acidente vascular cerebral em 30% em comparação com CRM com CEC, mas não

mostrou diferença em outros resultados. Novos ERCs foram publicados, indicando necessidade de nova meta-análise para investigar resultados agrupados adicionando esses estudos.

Métodos: MEDLINE, EMBASE, CENTRAL / CCTR, SciELO, LILACS, Google Scholar e listas de referências de artigos relevantes foram pesquisados para ERCs que compararam os resultados de 30 dias (mortalidade por todas as causas, infarto do miocárdio ou acidente vascular cerebral - AVC) entre CRM com CEC versus sem CEC até maio de 2012. As medidas sumárias principais foram o risco relativo (RR) com intervalo de confiança de 95% (IC) e os valores de P (considerado estatisticamente significativo quando $<0,05$). Os RR foram combinados entre os estudos usando modelo de efeito randômico de DerSimonian-Laird. Meta-análise e meta-regressão foram concluídas usando o software versão Meta-Análise Abrangente 2 (Biostat Inc., Englewood, Nova Jersey, EUA).

Resultados: Quarenta e sete ERCs foram identificados e incluíram 13.524 pacientes (6.758 sem CEC e 6.766 com CEC). Não houve diferença significativa entre CRM com CEC e sem CEC no RR de mortalidade em 30 dias ou infarto do miocárdio, mas houve diferença em favor da CRM sem CEC no desfecho AVC (RR 0,793, IC 95% 0,660-0,920, $P = 0,049$). Não foi observado importante heterogeneidade dos efeitos sobre qualquer resultado, mas observou-se um viés de publicação sobre o desfecho "AVC". Meta-regressão não demonstrou influência do sexo feminino, o número de pontes ou idade nos resultados.

Conclusão: CRM sem uso da CEC reduz a incidência de acidente vascular cerebral pós-operatória de 20,7% e não tem efeito significativo sobre a mortalidade ou infarto do miocárdio em comparação com CRM com CEC. Sexo do paciente, número de enxertos realizados e idade não parecem explicar o efeito de RM sem CEC sobre a mortalidade, infarto do miocárdio ou acidente vascular cerebral, respectivamente.

Descritores: Metanálise. Ponte de artéria coronária sem circulação extracorpórea. Ponte cardiopulmonar.

INTRODUCTION

Rationale

The most recent published meta-analysis examined randomized controlled trials (RCTs) comprising a total of 8,961 patients and showed that off-pump coronary artery bypass graft surgery (CABG) reduces the incidence of stroke by 30% compared with on-pump CABG, but showed no difference in 30-day mortality and myocardial infarction, which were not affected by age, gender or number of grafts [1]. After the publication of this meta-analysis [1], two new RCTs were published – CORONARY [2] and On-Off Study [3], which

contributed over 4,752 and 411 patients, respectively. This represents a substantial increase of new patient data available in literature from RCTs as compared to what already exists, which indicates the need for execution of a new meta-analysis to investigate the pooled results adding these further studies.

Our meta-analysis attempts to determine if there is any real difference between off-pump and on-pump CABG in terms of outcomes.

Objectives

We performed a meta-analysis and meta-regression of RCTs to compare off-pump CABG versus on-pump CABG,

according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [4].

METHODS

Eligibility criteria

Using PICOS strategy, studies were considered if: (1) population comprised patients undergoing CABG; (2) compared outcomes between off-pump versus on-pump CABG; (3) outcomes studied included 30-day mortality (all-cause), myocardial infarction or stroke; (4) were prospective randomized controlled trials. The exclusion criteria were: (1) concomitant surgical intervention other than CABG, (2) concomitant medical intervention in one but not both of the two groups, (3) zero events in both groups, so that they could not contribute to the pooled analysis for a specific outcome.

Information Sources

The following databases were used (until May 2012): MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL/CCTR), ClinicalTrials.gov, SciELO (Scientific Electronic Library Online), LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde – The Latin American and Caribbean Health Sciences), Google Scholar and reference lists of relevant articles.

Search

We conducted the search using Medical Subject Heading (MeSH) terms ('coronary artery bypass, off-pump' OR 'off-pump coronary artery bypass' OR 'off pump coronary artery bypass' OR 'off-pump' OR 'coronary artery bypass, beating heart' OR 'beating heart cardiopulmonary bypass' OR 'cardiopulmonary bypass' OR 'cardiopulmonary bypasses' OR 'bypass, cardiopulmonary' OR 'bypasses, cardiopulmonary') AND ('randomized controlled trial' OR 'clinical trial' OR 'controlled clinical trials, randomized' OR 'clinical trials, randomized' OR 'trials, randomized clinical').

Study Selection

The following steps were done: (1) identification of titles of records through databases searching; (2) removal of duplicates; (3) screening and selection of abstracts; (4) assessment for eligibility through full-text articles; (5) final inclusion in study.

One reviewer followed the steps 1 to 3. Two independent reviewers followed step 4 and selected studies. Inclusion or exclusion of studies was decided unanimously. When there was disagreement, a third reviewer took the final decision.

Data Items

The endpoints were Risk Ratio (RR) for 30-day mortality (all-cause), myocardial infarction and stroke after off-pump versus on-pump CABG.

Data Collection Process

Two independent reviewers extracted the data. When there was disagreement about data, a third reviewer (the first author) checked the data and took the final decision about it. From each study, we extracted patient characteristics, study design, and outcomes (number of events and number of total groups).

Risk of Bias in Individual Studies

Included studies were assessed for the following characteristics: (1) sequence generation, (2) allocation concealment, (3) blinding, (4) incomplete outcome data, (5) selective outcome reporting, and (6) other sources of bias. Taking these characteristics into account, the papers were classified into A (low risk of bias), B (moderate risk of bias) or C (high risk of bias).

Two independent reviewers assessed risk of bias. Agreement between the two reviewers was assessed using kappa statistics for full text screening, and rating of relevance and risk of bias. When there was disagreement about risk of bias, a third reviewer (the first author) checked the data and took the final decision about it.

Summary Measures

The principal summary measures were RR's with 95% Confidence Interval (CI) and *P* values (considered statistically significant when <0.05). The meta-analysis was completed using the software Comprehensive Meta-Analysis version 2 (Biostat Inc., Englewood, New Jersey, USA).

Synthesis of Results

Forest plots were generated for graphical presentations for clinical outcomes and we performed the I² test and Chi² test for assessment of heterogeneity across the studies [5]. Each study was summarized by the RR for off-pump CABG compared to on-pump CABG. The RR's were combined across studies using weighted DerSimonian-Laird random effects model [6]. The model was weighted by number of events in each study.

Risk of Bias Across Studies

To assess publication bias, a funnel plot was generated (for each outcome), being statistically assessed by Begg and Mazumdar's test [7] and Egger's test [8].

Meta-regression Analysis

Meta-regression analyses were performed to determine

whether the effects of off-pump CABG were modulated by pre-specified factors. Meta-regression graphs describe the effect of off-pump CABG on the outcome (plotted as a log RR on the y-axis) as a function of a given factor (plotted as a mean or proportion of that factor on the x-axis). Meta-regression coefficients show the estimated increase in log RR per unit increase in the covariate. Since log RR >0 corresponds to RR >1 and log RR <0 corresponds to RR <1, a negative coefficient would indicate that as a given factor increases, the RR decreases.

The pre-determined modulating factors to be examined were: sex (for mortality), number of bypass grafts (for myocardial infarction) and age (for stroke). Sex was represented as the proportion of females in the RCT. Number of bypass grafts was represented as the difference between the mean number of grafts (arterial and venous combined) performed in the off-pump CABG group minus the mean number of grafts performed in the on-pump CABG group in the RCT. Age was represented as the mean age of the patients participating in the RCT.

RESULTS

Study Selection

A total of 1110 citations were identified, of which 108 studies were potentially relevant and retrieved as full-text. Forty-seven [2,3,9-52] publications fulfilled our eligibility criteria. Interobserver reliability of study relevance was excellent (Kappa = 0.85). Agreement for decisions related to study validity was very good (Kappa = 0.81). The search strategy can be seen in Figure 1.

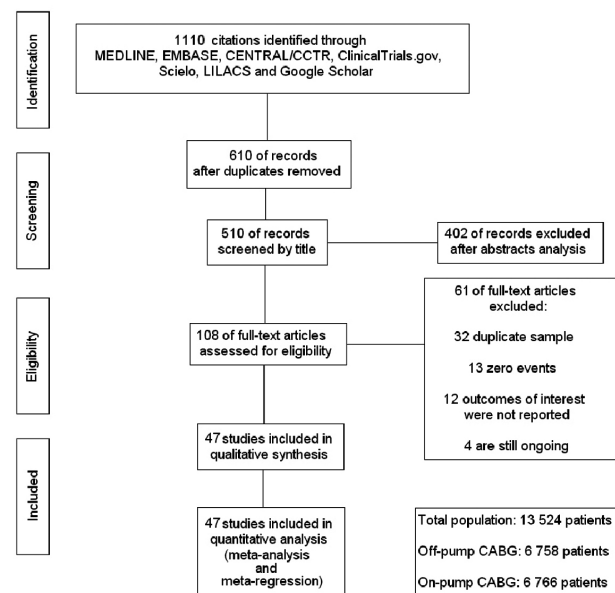


Fig. 1 - Flow diagram of studies included in data search

Study Characteristics

Characteristics of each study are shown in Table 1. A total of 13,524 patients were studied with 6,758 undergoing off-pump CABG and 6,766 undergoing on-pump CABG, including the years 2000 to 2012. We observed that most studies consisted of patients whose mean age was around the sixth decade of life, mostly male and on-pump CABG presenting higher mean coronary bypasses. The overall internal validity was considered moderate risk of bias.

Synthesis of Results

The RR of the risk of 30-day mortality in the off-pump group compared with on-pump group in each study is reported in Figure 2. There was no evidence for important heterogeneity of treatment effect among the studies for death. The overall RR (95% confidence interval) of 30-day mortality showed no statistical significant difference between off-pump CABG compared to on-pump CABG (random effect model: RR 0.938, 95% CI 0.731 to 1.203, $P = 0.612$).

The RR of the risk of myocardial infarction in the off-pump group compared with on-pump group in each study is reported in Figure 3. There was no evidence for important heterogeneity of treatment effect among the studies for myocardial infarction. The overall RR (95% confidence interval) of myocardial infarction showed no statistical significant difference between off-pump CABG compared to on-pump CABG (random effect model: RR 0.904, 95% CI 0.773 to 1.057, $P = 0.205$).

The RR of the risk of stroke in the off-pump group compared with on-pump group in each study is reported in Figure 4. There was no evidence for important heterogeneity of treatment effect among the studies for stroke. The overall RR (95% CI) of stroke showed statistical significant difference in favor to off-pump CABG compared to on-pump CABG (random effect model: RR 0.793, 95% CI 0.660 to 0.920, $P = 0.049$).

Risk of Bias Across Studies

Begg and Mazumdar's and Egger's tests did not reveal any evidence of publication bias, with the exception of stroke for which both tests were statistically significant (Figure 5).

Meta-regression Analysis

Meta-regression coefficients were not statistically significant for death and proportion of females (coefficient -0.02, 95% CI -0.05 to 0.01, $P = 0.103$), myocardial infarction and graft differential (coefficient -0.59, 95% CI -0.63 to 1.81, $P = 0.344$), stroke and mean age (coefficient 0.00, 95% CI -0.06 to 0.06, $P = 0.984$) - Figure 6.

Table 1. Study characteristics

Trial	Off-Pump (n)	On-Pump (n)	Age (mean)	Female Gender (%)	Off-Pump Grafts Per Patient (mean)	On-Pump Grafts Per Patient (mean)	Differential Number of Grafts Per Patient	Risk of Bias
CORONARY [2]	2375	2377	67.5	19.1	3.0	3.2	- 0.2	A
ON-OFF [3]	208	203	73.5	30.7	3.0	3.3	- 0.3	A
DOORS [9]	450	450	74.0	23.0	2.9	3.0	- 0.1	B
MASS III [10]	155	153	60.0	21.0	2.5	3.0	- 0.5	A
BBS [11]	176	163	75.4	35.5	3.2	3.3	- 0.1	A
ROOBY [12]	1104	1099	62.8	0.6	2.9	3.0	- 0.1	C
PRAGUE-11 [13]	40	40	66.0	20.0	1.9	2.4	- 0.5	B
JOCRI [14]	81	86	59.5	13.2	3.5	3.6	- 0.1	B
PRAGUE-4 [15]	204	184	62.5	18.8	2.3	2.7	- 0.4	B
SMART [16]	98	99	62.4	22.8	3.4	3.4	0.0	A
OCTOPUS [17]	142	139	61.3	28.5	2.4	2.6	- 0.2	B
BHACAS-1 [18]	100	100	62.0	19.5	2.4	2.5	- 0.1	B
BHACAS-2 [18]	100	101	62.5	16.4	2.9	3.0	- 0.1	B
Souza Uva et al. [19]	73	74	65.3	16.3	3.5	3.5	0.0	B
Fattouch et al. [20]	63	65	62.0	31.3	2.6	2.8	- 0.2	A
Medved et al. [21]	30	30	60.7	28.3	2.3	2.5	- 0.2	B
Tully et al. [22]	30	36	65.5	24.1	2.2	2.5	- 0.3	B
Hernandez Jr. et al. [23]	99	102	NR	19.9	3.2	3.2	0.0	B
Sajja et al. [24]	56	60	60.3	11.2	3.1	3.9	- 0.8	B
Motallebzadeh et al. [25]	108	104	64.5	10.8	NR	NR	NR	C
Al-Ruzzeh et al. [26]	84	84	63.1	16.1	2.7	2.8	- 0.1	A
Niranjan et al. [27]	40	40	66.9	17.5	3.9	3.8	0.1	B
Vedin et al. [28]	33	37	65.0	20.0	3.0	3.0	0.0	B
Cavalca et al. [29]	25	25	65.7	25.5	2.5	3.1	- 0.6	B
Paparella et al. [30]	15	16	NR	NR	2.7	3.3	- 0.4	B
Nesher et al. [31]	60	60	67.5	25.0	2.3	2.9	- 0.6	C
Rastan et al. [32]	20	20	64.2	20.0	3.0	2.9	0.1	B
Alwan et al. [33]	35	35	63.5	30.0	2.3	2.5	- 0.2	B
Gerola et al. [34]	80	80	59.0	34.4	1.7	1.8	- 0.1	B
Légaré et al. [35]	150	150	62.9	19.7	2.8	3.0	- 0.2	B
Lingaas et al. [36]	60	60	64.5	21.7	2.6	2.8	- 0.2	B
Khan et al. [37]	54	49	63.3	12.6	3.0	3.4	- 0.4	B
Motallebzadeh et al. [38]	15	20	63.9	8.6	2.2	3.2	- 1.0	B
Selvanayagam et al. [39]	30	30	60.5	13.3	2.8	2.9	- 0.1	B
Wehlin et al. [40]	21	16	64.9	18.9	3.0	2.5	0.5	B
Carrier et al. [41]	28	37	70.0	23.1	3.0	3.4	- 0.4	B
Lee et al. [42]	30	30	65.8	23.3	3.1	3.6	- 0.5	A
Sahlman et al. [43]	24	26	62.7	18.0	3.2	3.0	0.2	B
Muneretto et al. [44]	88	88	66.5	39.2	2.7	2.8	- 0.1	B
Smith et al. [45]	21	23	61.0	15.9	2.7	3.0	- 0.3	B
Baker et al. [46]	12	14	64.0	19.2	2.2	2.5	- 0.3	B
Covino et al. [47]	21	16	NR	10.8	1.5	1.8	- 0.3	C
Güler et al. [48]	19	18	56.0	NR	NR	NR	NR	C
Penttila et al. [49]	11	11	59.4	0.0	2.8	3.3	- 0.5	B
Diegeler et al. [50]	20	20	64.6	35.0	2.0	3.5	- 1.5	C
Kochamba et al. [51]	29	29	58.6	22.4	2.5	2.5	0.0	B
Wandschneider et al. [52]	41	67	65.4	21.3	2.3	3.1	- 0.8	B

A – Low risk of bias; B – Moderate risk of bias; C – High risk of bias; NR – non reported

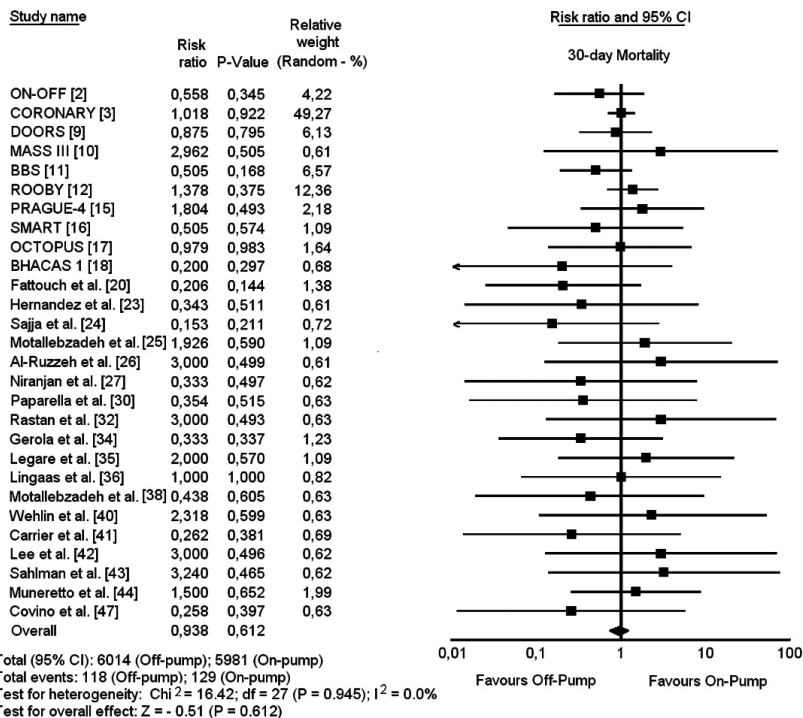


Fig. 2 - Risk ratio and conclusions plot of 30-day mortality associated with off-pump versus on-pump CABG

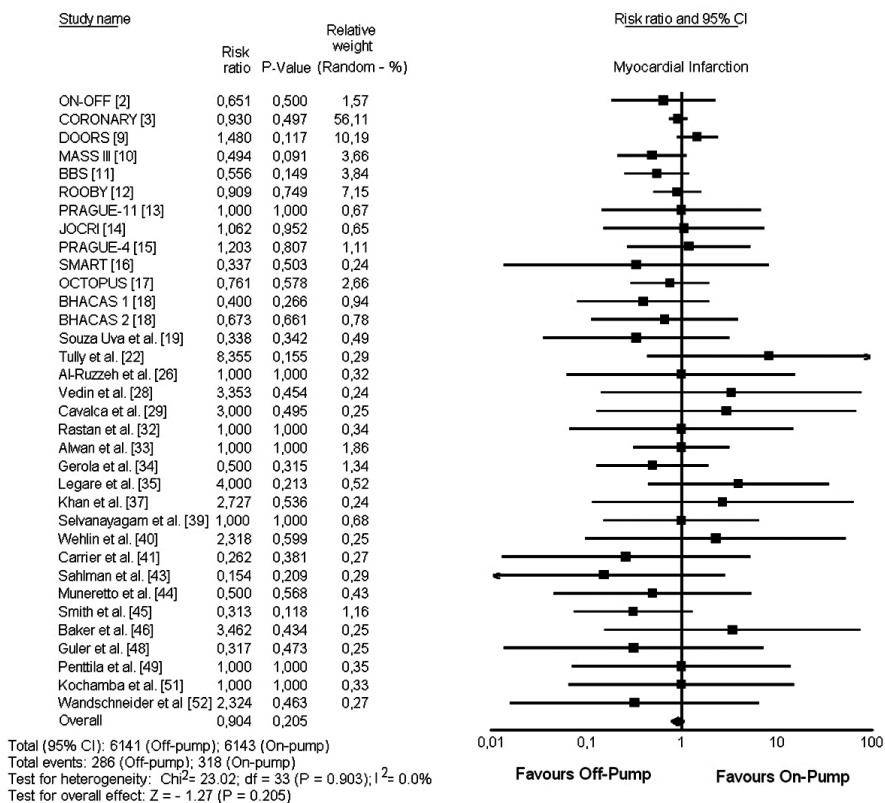


Fig. 3 - Risk ratio and conclusions plot of myocardial infarction associated with off-pump versus on-pump CABG

Study name	Risk ratio	P-Value	Relative weight (Random - %)
ON-OFF [2]	0,325	0,491	0,87
CORONARY [3]	0,890	0,675	29,61
DOORS [9]	0,556	0,131	15,26
MASS III [10]	0,494	0,411	3,13
BBS [11]	1,080	0,887	7,74
ROOBY [12]	1,742	0,208	11,85
JOCRI [14]	0,354	0,523	0,87
PRAGUE-4 [15]	0,180	0,268	0,96
SMART [16]	1,010	0,992	2,35
OCTOPUS [17]	0,489	0,558	1,55
BHACAS 1 [18]	0,667	0,653	2,83
BHACAS 2 [18]	0,337	0,342	1,76
Sousa Uva et al. [19]	0,203	0,300	0,97
Medved et al. [21]	0,500	0,563	1,61
Hernandez et al. [23]	0,147	0,203	1,02
Sajja et al. [24]	0,357	0,525	0,88
Motallebzadeh et al. [25]	0,321	0,322	1,75
Al-Ruzzeq et al. [26]	1,000	1,000	2,36
Nirajan et al. [27]	1,000	1,000	1,18
Niesher [31]	0,667	0,650	2,88
Legare et al. [35]	5,000	0,298	0,97
Lingaas et al. [36]	0,200	0,296	0,97
Motallebzadeh et al. [38]	0,438	0,605	0,90
Selvanayagam et al. [39]	0,333	0,496	0,89
Carrier et al. [41]	0,437	0,608	0,88
Lee et al. [42]	0,333	0,496	0,89
Sahlman et al. [43]	1,083	0,954	1,20
Muneretto et al. [44]	0,200	0,297	0,97
Diegeler et al. [50]	0,333	0,493	0,90
Overall	0,793	0,049	

Total (95% CI): 6188 (Off-pump); 6169 (On-pump)
 Total events: 73 (Off-pump); 104 (On-pump)
 Test for heterogeneity: $\chi^2 = 14.29$; $df = 28$ ($P = 0.985$); $I^2 = 0.0\%$
 Test for overall effect: $Z = -1.96$ ($P = 0.049$)

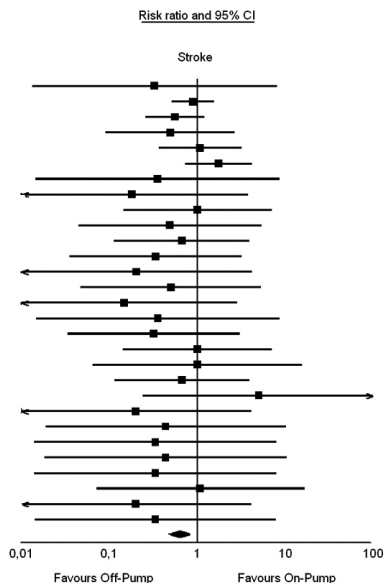


Fig. 4 - Risk ratio and conclusions plot of stroke associated with off-pump versus on-pump CABG

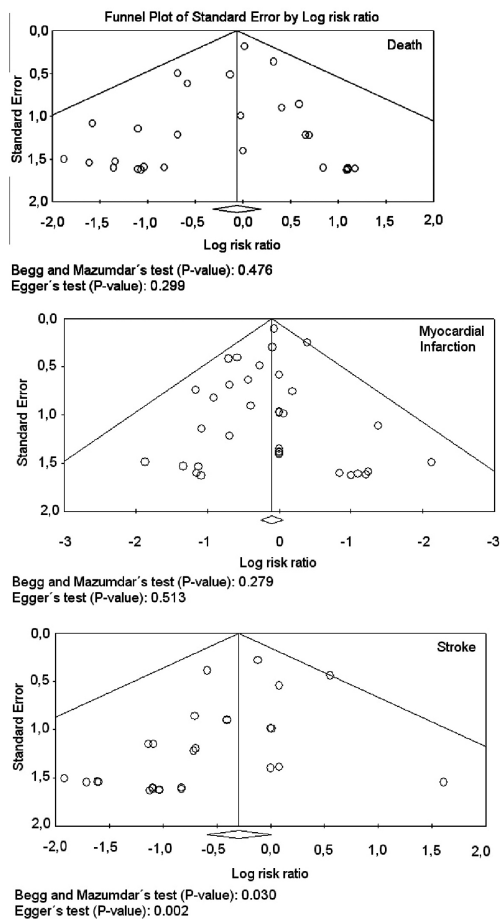


Fig. 5 - Publication bias analysis by funnel plot graphic for the outcomes

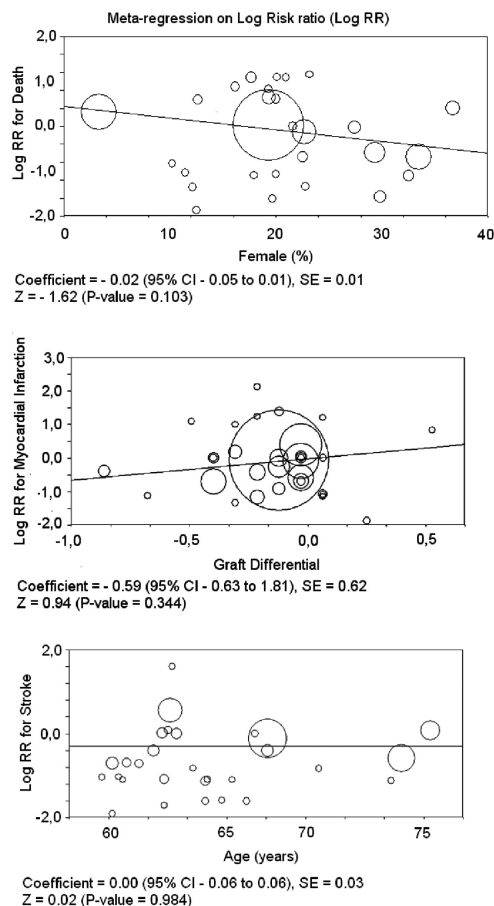


Fig. 6 - Meta-regression analysis by representative plots

DISCUSSION

Summary of Evidence

The results of this meta-analysis demonstrate that there was statistical significant difference in favor to off-pump CABG compared to on-pump CABG in RR for stroke and no difference about death or myocardial infarction, being the summary measures free from the influence of heterogeneity of the effects. Only the outcome “stroke” was under the influence of publication bias. Meta-regression did not demonstrate any influence of female gender, number of grafts performed and age on mortality, myocardial infarction or stroke, respectively.

Considerations about this Meta-Analysis

To our knowledge, this is the largest meta-analysis of RCTs performed to date, providing incremental value by demonstrating that off-pump CABG reduces the incidence of post-operative stroke compared with on-pump CABG. Furthermore, this analysis confirms that off-pump CABG does not significantly reduce the incidence of short-term all-cause mortality and post-operative myocardial infarction. The potential benefits of off-pump CABG on these outcomes do not appear to be determined by patient gender, number of grafts performed or age.

The effect of off-pump CABG on stroke has been a polemical topic, with most reports showing no beneficial effect [53-55]. The two largest trials to date – CORONARY [2] with 4,752 patients and ROOBY [12] with 2,143 patients – showed no effect or trend for reduction in stroke. The most recent trial published – On-Off Study with 411 patients – also did not show any benefit on incidence of stroke. Afilalo et al. [1] emphasize that it would take more than 10,000 patients in a trial to obtain a probabilistic sample and detect statistically significant differences regarding the outcome “stroke”, which explains why no trial to date has been able to demonstrate substantial differences between the groups regarding this outcome. Something that could explain the lower incidence of stroke in off-pump CABG is less manipulation of the aorta in comparison to on-pump CABG. El Zayat et al. [56] demonstrated in a RCT the importance of avoiding clamp during off-pump CABG using clampless facilitating devices to reduce cerebral embolic events, which proves that the less manipulation of the aorta decreases the incidence of stroke.

According to some authors [57,58], female and elderly patients are thought to face higher risks associated with on-pump CABG and therefore benefit more from off-pump CABG. The meta-regression analysis in this study refutes these hypotheses that differences in study population are responsible for the treatment effects observed across trials.

Although other meta-analyses have been published on this field, this analysis is important for some reasons.

The pooled sample size was 66% larger than the largest previous published meta-analysis [1]. Our larger sample size translated into greater statistical power and precision, reducing the amount of uncertainty surrounding treatment effects. Two recently published trials – CORONARY [2] and On-Off Study [3] – had not been included in the largest prior meta-analysis and were included in this analysis (published in 2012 and contributed 5,163 out of the 13,524 patients). Our meta-analysis summarized the results of best studies in medical literature regarding hard outcomes, strengthening the concept of off-pump CABG. Furthermore, the meta-regression enhances consistency of pooled results.

Risk of Bias and Limitations

This meta-analysis did not included data from nonrandomized and/or observational studies, which reflects the “real world”, but they are limited by treatment bias, confounders, and a tendency to overestimate treatment effects. Patient selection alters outcome and thus makes nonrandomized studies obviously less robust.

Although it was not observed statistical heterogeneity between trials, the differences in terms of operative technique and volume may have led to an influence of clinical heterogeneity not capable of perception by meta-analysis. Other factors not taken into consideration, for not being reported in trials and that may influence results, are the level of manipulation of the aorta and the level of atheromatosis of the aortic wall, which favors embolic cerebrovascular events during partial clamping.

There are inherent limitations with meta-analyses, including the use of cumulative data from summary estimates. Patient data were gathered from published data, not from individual patient follow-up. Access to individual patient data would have enabled us to conduct further subgroup analysis and propensity analysis to account for differences between the treatment groups.

CONCLUSIONS

Off-pump CABG reduces the incidence of post-operative stroke by 20.7% and has no substantial effect on mortality or myocardial infarction in comparison to on-pump CABG. Patient gender, number of grafts performed and age do not appear to explain the effect of off-pump CABG on mortality, myocardial infarction or stroke, respectively.

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