Off-Pump Coronary Artery Bypass May Increase Late Mortality: A Meta-Analysis of Randomized Trials

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Background. Although a lot of randomized trials of off-pump coronary artery bypass grafting (CABG) versus on-pump CABG were conducted, the majority of them reported only early outcomes. Previous meta-analyses of a few randomized trials found no differences for 1-year to 2-year mortality.

Methods. We focused late (≥1 year) all-cause mortality and performed a meta-analysis of randomized controlled trials of off-pump versus on-pump CABG. The MEDLINE, the EMBASE, and the Cochrane Central Register of Controlled Trials were searched using PubMed and OVID. For each study, data regarding all-cause mortality in both the off-pump and on-pump groups were used to generate risk ratios (RRs) and 95% confidence intervals. Study-specific estimates were combined using inverse variance-weighted averages of logarithmic RRs in both fixed-effects and random-effects models.

Results. Our search identified 11 results of 12 randomized trials (4,326 patients) of off-pump versus on-pump CABG. Pooled analysis demonstrated a statistically significant increase in midterm all-cause mortality by a factor of 1.37 with off-pump relative to on-pump CABG (RR, 1.373; 95% confidence interval, 1.043 to 1.808). Exclusion of any single result, except for the largest (>2,000 patients) trial, from the analysis did not substantively alter the overall result of our analysis. Eliminating the largest trial demonstrated a statistically nonsignificant benefit of on-pump over off-pump CABG for midterm all-cause mortality (RR, 1.344; 95% confidence interval, 0.952 to 1.896).

Conclusions. The results of our analysis suggest that off-pump CABG may increase late all-cause mortality by a factor of 1.37 over on-pump CABG. Longer term mortality from randomized trials of off-pump versus on-pump CABG is needed.

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Although many randomized controlled trials of off-pump coronary artery bypass grafting (CABG) versus on-pump CABG have been conducted, the majority reported only early outcomes. In previous meta-analyses [1, 2] of a few randomized controlled trials, no difference was found for 1-year to 2-year mortality. Since these meta-analyses were performed, however, a number of randomized controlled trials have provided 1-year or greater mortality. In several meta-analyses of randomized controlled trials, patients undergoing off-pump CABG had a lower rate of revascularization [1, 3–5] and lower graft patency [4, 6, 7] than did patients undergoing on-pump CABG. The most recently published large randomized controlled trial [8] showed that 1-year composite outcomes (death from any cause within 1 year, nonfatal myocardial infarction between 30 days and 1 year, or repeat revascularization between 30 days and 1 year), completeness of revascularization, and graft patency were significantly worse with off-pump than with on-pump CABG. Incomplete revascularization and attenuated graft patency in off-pump CABG might affect late mortality. Meanwhile, the trial [8] showed a trend toward more deaths from cardiac causes at 1 year in the off-pump group than in the on-pump group and no significant difference in more than 5-year survival (by Kaplan-Meier analysis for death from any cause) between off-pump and on-pump treatments. We focused late (≥1-year) all-cause mortality and performed a meta-analysis of randomized controlled trials of off-pump versus on-pump CABG.

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Material and Methods

Search Strategy

All prospective randomized controlled trials of off-pump versus on-pump CABG with 1-year or greater follow-up were identified using a 2-level search strategy. First, public domain databases including the MEDLINE, the EMBASE, and the Cochrane Central Register of Controlled Trials were searched using Web-based search engines (PubMed, OVID). Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles and a search of reviews and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analysis.

The MEDLINE database was searched from January 1966 to November 2009. The medical subject headings keywords included coronary artery bypass, off-pump, randomized controlled trial, and clinical trial. The Cochrane Library and Central Register of Controlled Trials (current through the November 2009) was searched using

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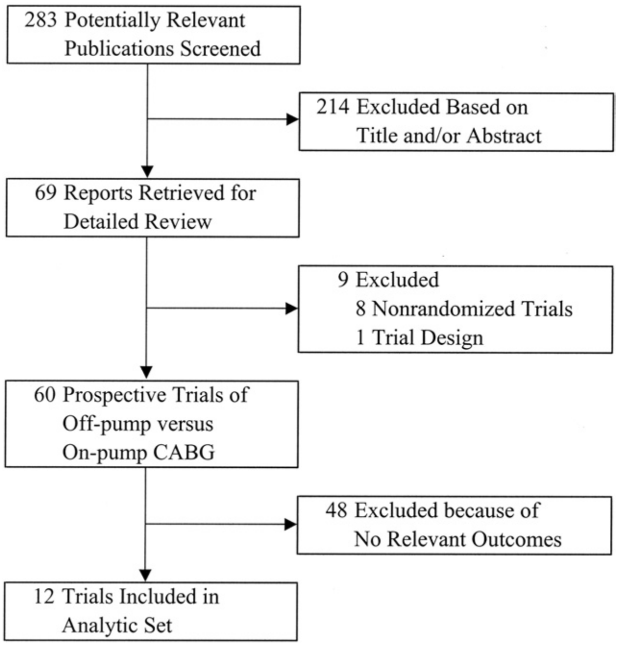

Fig 1. Quality of reporting of meta-analyses [9] flow diagram for the meta-analysis. (CABG = coronary artery bypass grafting.)

OVID exploding keywords including off-pump, clinical trial, and randomized clinical trial. The EMBASE database was searched from January 1991 to November 2009 using OVID exploding keywords including off-pump and clinical trial.

Study Selection

Studies considered for inclusion met the following criteria: the design was a prospective randomized controlled clinical trial; patients were randomly assigned to off-pump versus on-pump CABG; and main outcomes included 1-year or greater all-cause mortality. A quality of reporting of meta-analyses [9] flow diagram of the study selection process is illustrated in Figure 1.

Quality Assessment and Data Abstraction

All qualifying studies were assessed for adequate blinding of randomization, completeness of follow-up, and objectivity of the outcome assessment. Blinding of the interventions was not used for quality assessment because both the interventions (off-pump and on-pump CABG) were surgical. Data regarding detailed inclusion criteria, duration of follow-up, rates of crossover, and all-cause mortality were abstracted (as available) from each individual study.

Statistical Analysis

For each study, data regarding all-cause mortality in both the off-pump and on-pump groups were used to generate risk ratios (RRs) (>1, favors on-pump CABG; <1, favors off-pump CABG) and 95% confidence intervals (CI). Study-specific estimates were combined using inverse variance-weighted averages of logarithmic RRs in both fixed-effects and random-effects models. Between-study heterogeneity was analyzed by means of standard χ^2 tests. Where no significant statistical heterogeneity was identified, the fixed-effects estimate was used preferentially as the summary measure. Sensitivity analyses were performed to assess the contribution of each result to the pooled estimate by excluding individual outcomes one at a time and recalculating the pooled RR estimates for the remaining results (leave-one-out meta-analysis). To assess the impact of differential length of follow-up on the pooled estimate, meta-regression was conducted for the RR and duration of follow-up using an unrestricted maximum likelihood model. Publication bias was assessed graphically using a funnel plot and mathematically using an adjusted rank-correlation test [10]. All analyses were conducted using Meta-Analyst version 3.0 [11] and Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

Results

As outlined in Figure 1, our search identified 11 results (≥1-year all-cause mortality) of 12 prospective randomized controlled clinical trials of off-pump versus on-pump CABG [8, 12–25]. Angelini and colleagues [12] combined and updated mortality in the Beating Heart Against Cardioplegic Arrest Study 1 and 2 [13]. Mortality in the Octopus trial [23] was updated by van Dijk and colleagues [22]. Two additional outcomes (not included in the most resent meta-analysis by Feng and colleagues [2]) were identified from the Best Bypass Surgery trial by Jensen and colleagues [15] and the Randomized On/Off Bypass (ROOBY) trial by Shroyer and colleagues [8]. In total, our meta-analysis included data on 4,326 patients randomized to off-pump or on-pump CABG. The duration of follow-up varied from 1 year to greater than 6 years. In Table 1, summary measures of methodologic quality for each trial are outlined and the baseline characteristics for the patients enrolled in each trial are summarized.

Eight of the 11 individual results demonstrated a statistically nonsignificant benefit of on-pump over off-pump CABG for late all-cause mortality. Pooled analysis of the 11 results demonstrated a statistically significant increase in late all-cause mortality by a factor of 1.37 with off-pump relative to on-pump CABG in fixed-effects models (RR, 1.373; 95% CI, 1.043 to 1.808; $p = 0.024$; Fig 2). There was minimal trial heterogeneity ($p = 0.999$) and accordingly no difference in the pooled result from random-effects modeling. Exclusion of any single result, except for the ROOBY trial by Shroyer and colleagues [8], from the analysis (leave-one-out meta-analysis) did not substantively alter the overall result of our analysis (Fig 3). Eliminating the ROOBY trial, the largest (>2,000 patients) one, demonstrated a statistically nonsignificant benefit of on-pump over off-pump CABG for late all-cause mortality (fixed-effects RR, 1.344; 95% CI, 0.952 to 1.896; $p = 0.093$). There was no statistically significant linear relationship between the log RR and duration of follow-up ($p = 0.81871$; Fig 4). To assess publication bias

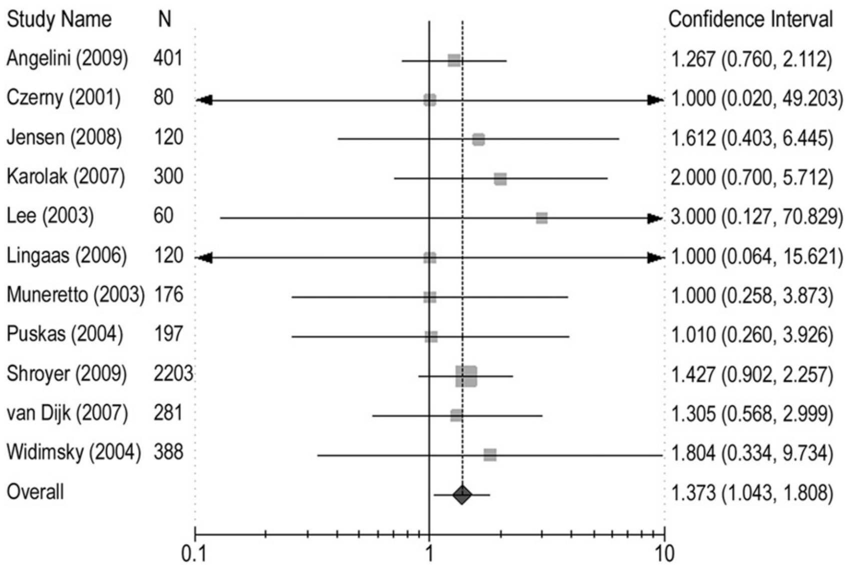

Fig 2. Forest plot (graphic display of findings of systematic reviews and meta-analyses) of late all-cause mortality among patients randomized to off-pump versus on-pump coronary artery bypass grafting. Gray boxes represent risk ratio.

we generated a funnel plot of the logarithm of effect size versus the inverse standard error for each result (Fig 5). There was no evidence of significant publication bias ($p = 0.64043$).

Comment

The results of our analysis suggest that off-pump CABG may increase late (≥1 year) all-cause mortality by a factor of 1.37 over on-pump CABG. Previous meta-analyses [1, 2] of a few randomized controlled trials, however, found no difference for 1-year to 2-year mortality. In the meta-analysis by Wijeysundera and colleagues [1] of 4 trials, off-pump CABG was associated with a trend toward reduced 1-year to 2-year mortality (odds ratio [OR], 0.82; 95% CI, 0.40 to 1.68; $p = 0.59$). The more recent meta-analysis by Feng and colleagues [2] of 8 trials showed that off-pump CABG did not reduce 1-year all-cause mortality (OR, 1.00; 95% CI, 0.75 to 1.33; $p = 1.00$). Although the sensitivity analysis in the present meta-analysis revealed that the ROOBY trial [8] strongly contributed to the pooled estimate, the previous meta-analyses [1, 2] did not include it. In the ROOBY trial, 2,203 patients underwent randomization, and 53 attending surgeons at 18 participating centers were involved, though the majority of previous trials have included smaller patient cohorts, a smaller number of participating centers, or both [3]. The primary long-term composite endpoint of the ROOBY trial was death from any cause within 1 year, nonfatal myocardial infarction between 30 days and 1 year, or repeat revascularization between 30 days and 1 year. Although no significant difference was found for death from any cause (4.1% vs 2.9%; RR, 1.41; 95% CI, 0.90 to 2.24; $p = 0.15$), there were significantly more deaths from

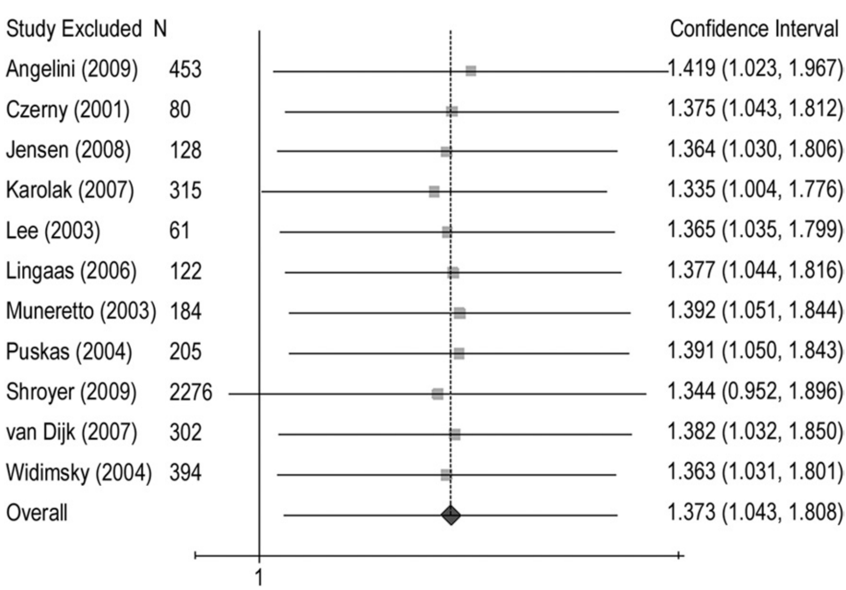

Fig 3. Leave-one-out meta-analysis excluding individual results one at a time and recalculating the pooled risk ratio (gray boxes) estimates for the remaining results.

Table 1. Baseline Patient Characteristics and Methodologic Quality for Each Trial

Characteristic	Angelini (2009) [12] Angelini (2002) [13] BHACAS 1	BHACAS 2	Czerny (2001) [14]	Jensen (2008) [15] BBS
No. randomized	200	201	80	120
Duration of follow-up (years)	6.3 ± 1.7		1.1 ± 0.5	1
Inclusion criteria of CABG	NR	NR	Elective	Elective or subacute
Demographics				
Age (years)	62 ± 9	62 ± 9	64 ± 10	75 ± 5[a]
Male (%)	81	84	84	61[a]
LVEF	<0.50: 21%[b]	<0.50: 23%[b]	0.64 ± 0.10	0.50 ± 0.09[a]
Design				
Primary end point at follow-up	Clinical outcomes, HRQoL, graft patency		(Completeness of revascularization[c])	Cognitive dysfunction
Mortality (%)				
On-pump	11.4 (1.5 at 1 year)		0	5.1
Off-pump	14.5 (1.0 at 1 year)		0	8.2
Internal validity				
Follow-up (%)	100		NR	NR
Crossovers (%)				
To on-pump	2	0	23	7
To off-pump	0	0	0	2
Intent-to-treat	Yes		Yes	Yes
Events committee	NR		NR	Blinded

Characteristic	Karolak (2007) [16] Légaré (2004) [17]	Lee (2003) [18]	Lingaas (2006) [19]
No. randomized	300	60	120
Duration of follow-up (years)	Median, 3.8 (IQR, 3.4–4.4)	1.1 ± 0.2	1
Inclusion criteria of CABG	Nonemergency	Primary elective	NR
Demographics			
Age (years)	63 ± 10	66 ± 10	65 ± 8
Male (%)	80	77	78
LVEF	0.30–0.550: 14%[b]	0.55 ± 0.10	0.72 ± 0.10
Design			
Primary end point at follow-up	Death, readmission for cardiac cause	Neurocognitive function, clinical morbidity	Clinical and angiographic results
Mortality (%)			
On-pump	3.3	0	1.7
Off-pump	6.7	3.3	1.7
Internal validity			
Follow-up (%)	99.7	100	98
Crossovers (%)			
To on-pump	13	0	12
To off-pump	1	0	0
Intent-to-treat	Yes	No crossovers	Yes
Events committee	NR	Blinded	Blinded

Continued

Table 1. Continued

Characteristic	Muneretto (2003) [20]	Puskas (2004) [21] SMART	Shroyer (2009) [8] ROOBY
No. randomized	176	197	2,203
Duration of follow-up (years)	1.3 ± 1.0	1	1
Inclusion criteria of CABG	Elective	Primary elective	Elective or urgent
Demographics			
Age (years)	67 ± 9	62 ± 10	63 ± 9
Male (%)	61	77	99
LVEF	<0.30: 10%[b]	<0.45: 26%[b]	<0.45: 17%[b]
Design			
Primary end point at follow-up	Death, angina recurrence, MI, reintervention, graft patency	Graft patency	Composite of death, nonfatal MI, reintervention
Mortality (%)			
On-pump	4.5	4.0	2.7
Off-pump	4.5	4.1	3.9
Internal validity			
Follow-up (%)	NR	94	96
Crossovers (%)			
To on-pump	(9[d])	1	12
To off-pump	0	3	4
Intent-to-treat	Yes	Yes	Yes
Events committee	NR	NR	NR

Characteristic	van Dijk (2007) [22] Nathoe (2003) [23] Octopus	Widimsky (2004) [24] Straka (2004) [25] PRAGUE-4
No. randomized	281	388
Duration of follow-up (years)	5	1
Inclusion criteria of CABG	Primary nonemergency	Nonemergency
Demographics		
Age (years)	61 ± 9	Median, 63/62
Male (%)	68	81
LVEF	NR	≤0.50: 19%[b]
Design		
Primary end point at follow-up	Cognitive outcomes	Graft patency
Mortality (%)		
On-pump	6.5 (1.4 at 1 year)	1.1
Off-pump	8.5 (1.4 at 1 year)	2.0
Internal validity		
Follow-up (%)	99	100
Crossovers (%)		
To on-pump	7	15
To off-pump	4	7
Intent-to-treat	Yes	Yes
Events committee	Blinded	NR

[a] Values of 90 patients who were available for 1-year follow-up of cognitive dysfunction. [b] Percentage of patients. [c] Early primary end point. [d] Conversion to on-pump beating coronary artery bypass grafting.

BBS = best bypass surgery; BHACAS = Beating Heart Against Cardioplegic Arrest Study; CABG = coronary artery bypass grafting; HRQoL = health-related quality of life; IQR = interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; ROOBY = Randomized On/Off Bypass; SMART = surgical management of arterial revascularization therapies.

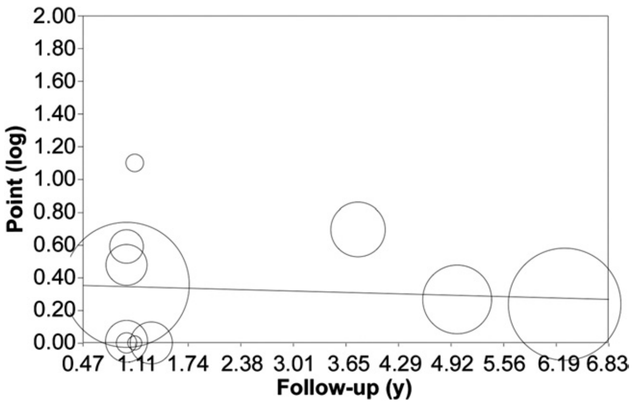

Fig 4. Meta-regression for duration of follow-up on the logarithm of point estimate (risk ratio). Each result is represented by a circle proportional to its weight in the analysis.

cardiac causes in the off-pump group than in the on-pump group (2.7% vs 1.3%; RR, 2.05; 95% CI, 1.09 to 3.86; $p = 0.03$). Meanwhile, a few observational studies provided risk-adjusted late mortality. In the meta-analysis by Wijeysundera and colleagues [1], 2 observational studies reporting risk-adjusted effects on long-term outcomes [26, 27] showed essentially no change in mortality (OR, 1.01; 95% CI 0.74 to 1.40; $p = 0.93$). Furthermore, recent large observational studies also demonstrated no difference in risk-adjusted late survival [28, 29].

The negative impact of incomplete revascularization and lower graft patency on late mortality rates has been suggested. Osswald and colleagues [30] focused on beneficial or jeopardizing effects of complete versus incomplete revascularization in 859 elderly (75 and older) patients. Mortality until 180 days after CABG was higher (24%) after incomplete than after complete revascularization (15%; $p = 0.005$). By logistic multivariable regression, incomplete revascularization was identified as an independent risk factor for death (OR, 1.8; $p = 0.015$). From the Coronary Artery Surgery Study Registry (3-vessel coronary disease), a retrospective analysis of 3,372 nonrandomized surgical patients was performed by Bell and colleagues [31]. In patients having class I or II angina (Canadian Cardiovascular Society criteria), adjusted cumulative 4-year survivals according to the number of vessels bypassed were 85% (1 vessel), 94% (2 vessels), 96% (3 vessels), and 96% (more than 3 vessels) ($p = 0.022$). Placing grafts to 3 or more vessels was independently associated with improved survival (RR, 0.745; 95% CI, 0.591 to 0.940; $p = 0.0132$) in patients having class III or IV angina. Kozower and colleagues [32] endeavored to determine how complete revascularization influenced long-term (51 ± 41 months) survival after CABG in 500 octogenarians. Multivariate regression analysis identified incomplete revascularization to be an independent predictor of late death (OR, 1.3; 95% CI, 0.8 to 2.1: $p = 0.01$). Excluding operative deaths, mean survival was 82 months with complete revascularization compared with 65 months with incomplete revascularization ($p = 0.008$). Survival was 62 ± 3% with complete versus 45 ± 6% with incomplete revascularization at 5 years, and 39 ± 3% with complete versus 25 ± 6% with incomplete revascularization at 8 years ($p = 0.008$). Synnergren and colleagues [33] analyzed the influence of incomplete revascularization on long-term (5.0 ± 2.8 years) mortality after CABG in 9,408 patients. Leaving 2 vascular segments without a bypass graft in 3-vessel disease was associated with an increased hazard ratio for death (1.82; 95% CI, 1.15 to 2.85; $p = 0.01$). Aziz and colleagues [34] aimed to clarify 580 octogenarian long-term survival rates by stratifying revascularization subtypes. Late survival was similar between functional (mean, 6.8 years) and traditional (6.7 years) complete revascularization ($p = 0.51$), but diminished with incomplete revascularization (4.2 years) ($p = 0.007$). Survival by group at 5 years was 59 ± 3% functional complete, 57 ± 4% traditional complete, and 45 ± 5% incomplete. Survival at 8 years was 40 ± 3% functional complete, 37 ± 4% traditional complete, and 26 ± 5% incomplete. Survival including only patients with survival greater than 12 months was again impaired with incomplete revascularization ($p = 0.04$). Meanwhile, lower graft patency as well as incomplete revascularization may impair late survival. A review of the literature by Ascione and colleagues [35] confirmed that clinical and angiographic outcome of CABG using bilateral internal mammary arteries was superior to that using a single (left) internal mammary artery with supplemental vein grafts. Better patency of a right internal mammary artery than vein grafts [36, 37] could contribute to improved survival [37, 38].

There has been the best evidence of lower revascularization rates [1, 3–5] and graft patency [4, 6, 7] in off-pump than on-pump CABG from meta-analyses of randomized controlled trials. A meta-analysis by Cheng and colleagues of 22 trials [3] demonstrated the lower mean number of distal vessels anastomosed (2.6 ± 0.6 vs 2.8 ± 0.7 for off-pump versus on-pump CABG; mean difference, −0.2; 95% CI, −0.3 to −0.1; $p = 0.0001$). In a meta-analysis by Wijeysundera and colleagues of 24 trials [1], the mean graft number was 0.19 lower in the

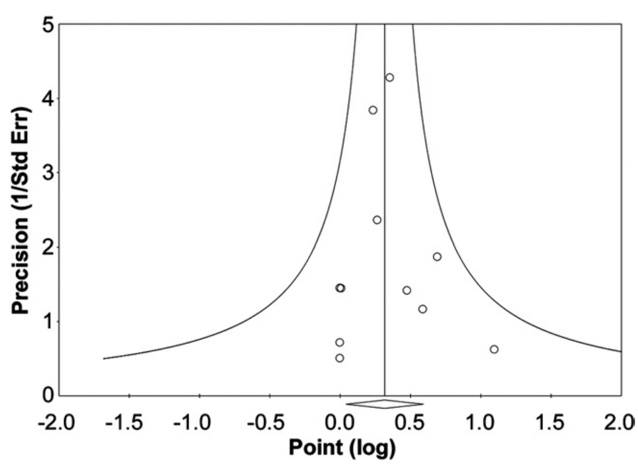

Fig 5. Funnel plot of the logarithm of point estimate (risk ratio) versus the inverse standard error for each result (circles).

off-pump CABG arm (95% CI, 0.25 lower to 0.13 lower; $p < 0.00001$). A meta-analysis by Møller and colleagues of 41 trials [5] found that significantly fewer distal anastomoses were performed after off-pump CABG (mean difference, −0.29, 95% CI, −0.46 to −0.13). In a meta-analysis by Lim and colleagues of 6 trials [4], patients undergoing off-pump CABG had a lower rate of revascularization (standardized mean difference, −0.164; 95% CI, −0.286 to −0.043; $p = 0.008$) and lower graft patency (RR for patency, 0.953; 95% CI, 0.927 to 0.980; $p = 0.001$) than did patients undergoing on-pump CABG. Cumulative analysis by Parolari and colleagues of 5 trials [6] documented a reduction in postoperative patency of grafts performed during off-pump CABG procedures (OR for occlusion, 1.51; 95% CI, 1.15 to 1.99; $p = 0.003$). Our previous meta-analysis [7] of 6 trials reporting 3-month or greater graft patency also demonstrated an increase in graft occlusion with off-pump relative to on-pump CABG (RR for occlusion, 1.27; 95% CI, 1.03 to 1.56; $p = 0.0234$; risk difference for occlusion, 3.0%; 95% CI, 0.6% to 5.4%; $p = 0.0129$). Furthermore, our most recently updated meta-analysis [39] of 8 results (6,898 grafts) of 9 trials (including the ROOBY trial) confirmed that off-pump CABG increased graft occlusion by 32% over on-pump CABG (RR for occlusion, 1.32; 95% CI, 1.18 to 1.48; $p < 0.00001$).

With the evidence of lower revascularization rate and graft patency in off-pump CABG patients, and the negative impact of incomplete revascularization and attenuated graft patency on late mortality rates, the finding of the present meta-analysis, worse late mortality in off-pump CABG, is never surprising. Although the meta-regression analysis revealed no influence of follow-up durations on risk estimates, 8 of 12 trials included in the present meta-analysis provided only 1-year mortality. To confirm our results, longer-term mortality from large randomized controlled trials of off-pump versus on-pump CABG is needed. Our analysis must be viewed in the context of its limitations. First, only data from randomized controlled trials were used, and patients enrolled in randomized trials may not be representative of patients typically seen in clinical practice. Because randomized trials balance both known and unknown confounders across treatment groups, however, this is the study design least vulnerable to bias. Second, a publication bias favoring off-pump CABG may influence our results. This risk was minimized through an exhaustive search of the available literature. Although publication bias was not indicated by the statistical tests, there is clearly limited power to detect such bias given the small number of studies examined. Despite these acknowledged limitations, we found that, based on a meta-analysis, on-pump CABG is likely effective in prevention of late all-cause mortality, and on-pump rather than off-pump CABG should be considered for patients who meet the criteria for enrollment in the randomized trials because mortality reduction must imply the greatest clinical benefit among patients undergoing CABG.

References

1. Wijeysundera DN, Beattie WS, Djaiani G, et al. Off-pump coronary artery surgery for reducing mortality and morbidity: meta-analysis of randomized and observational studies. J Am Coll Cardiol 2005;46:872–82.
2. Feng ZZ, Shi J, Zhao XW, Xu ZF. Meta-analysis of on-pump and off-pump coronary arterial revascularization. Ann Thorac Surg 2009;87:757–65.
3. Cheng DC, Bainbridge D, Martin JE, Novick RJ; Evidence-Based Perioperative Clinical Outcomes Research Group. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. Anesthesiology 2005;102:188–203.
4. Lim E, Drain A, Davies W, Edmonds L, Rosengard BR. A systematic review of randomized trials comparing revascularization rate and graft patency of off-pump and conventional coronary surgery. J Thorac Cardiovasc Surg 2006;132:1409–13.
5. Møller CH, Penninga L, Wetterslev J, Steinbrüchel DA, Gluud C. Clinical outcomes in randomized trials of off- vs. on-pump coronary artery bypass surgery: systematic review with meta-analyses and trial sequential analyses. Eur Heart J 2008;29:2601–16.
6. Parolari A, Alamanni F, Polvani G, et al. Meta-analysis of randomized trials comparing off-pump with on-pump coronary artery bypass graft patency. Ann Thorac Surg 2005;80:2121–5.
7. Takagi H, Tanabashi T, Kawai N, Kato T, Umemoto T. Off-pump coronary artery bypass sacrifices graft patency: meta-analysis of randomized trials. J Thorac Cardiovasc Surg 2007;133:e2–3.
8. Shroyer AL, Grover FL, Hattler B, et al. On-pump versus off-pump coronary-artery bypass surgery. N Engl J Med 2009;361:1827–37.
9. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999;354:1896–900.
10. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
11. Wallace BC, Schmid CH, Lau J, Trikalinos TA. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. BMC Med Res Methodol 2009;9:80.
12. Angelini GD, Culliford L, Smith DK, et al. Effects of on- and off-pump coronary artery surgery on graft patency, survival, and health-related quality of life: long-term follow-up of 2 randomized controlled trials. J Thorac Cardiovasc Surg 2009;137:295–303.
13. Angelini GD, Taylor FC, Reeves BC, Ascione R. Early and midterm outcome after off-pump and on-pump surgery in Beating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2): a pooled analysis of two randomised controlled trials. Lancet 2002;359:1194–9.
14. Czerny M, Baumer H, Kilo J, et al. Complete revascularization in coronary artery bypass grafting with and without cardiopulmonary bypass. Ann Thorac Surg 2001;71:165–9.
15. Jensen BØ, Rasmussen LS, Steinbrüchel DA. Cognitive outcomes in elderly high-risk patients 1 year after off-pump versus on-pump coronary artery bypass grafting. A randomized trial. Eur J Cardiothorac Surg 2008;34:1016–21.
16. Karolak W, Hirsch G, Buth K, Légaré JF. Medium-term outcomes of coronary artery bypass graft surgery on pump versus off pump: results from a randomized controlled trial. Am Heart J 2007;153:689–95.
17. Légaré JF, Buth KJ, King S, et al. Coronary bypass surgery performed off pump does not result in lower in-hospital morbidity than coronary artery bypass grafting performed on pump. Circulation 2004;109:887–92.

18. Lee JD, Lee SJ, Tsushima WT, et al. Benefits of off-pump bypass on neurologic and clinical morbidity: a prospective randomized trial. Ann Thorac Surg 2003;76:18–26.
19. Lingaas PS, Hol PK, Lundblad R, et al. Clinical and radiologic outcome of off-pump coronary surgery at 12 months follow-up: a prospective randomized trial. Ann Thorac Surg 2006;81:2089–95.
20. Muneretto C, Bisleri G, Negri A, et al. Off-pump coronary artery bypass surgery technique for total arterial myocardial revascularization: a prospective randomized study. Ann Thorac Surg 2003;76:778–83.
21. Puskas JD, Williams WH, Mahoney EM, et al. Off-pump vs conventional coronary artery bypass grafting: early and 1-year graft patency, cost, and quality-of-life outcomes: a randomized trial. JAMA 2004;291:1841–9.
22. van Dijk D, Spoor M, Hijman R, et al. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. JAMA 2007;297:701–8.
23. Nathoe HM, van Dijk D, Jansen EW, et al. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. N Engl J Med 2003;348:394–402.
24. Widimsky P, Straka Z, Stros P, et al. One-year coronary bypass graft patency: a randomized comparison between off-pump and on-pump surgery angiographic results of the PRAGUE-4 trial. Circulation 2004;110:3418–23.
25. Straka Z, Widimsky P, Jirasek K, et al. Off-pump versus on-pump coronary surgery: final results from a prospective randomized study PRAGUE-4. Ann Thorac Surg 2004;77: 789–93.
26. Boening A, Friedrich C, Hedderich J, Schoettler J, Fraund S, Cremer JT. Early and medium-term results after on-pump and off-pump coronary artery surgery: a propensity score analysis. Ann Thorac Surg 2003;76:2000–6.
27. Sabik JF, Blackstone EH, Lytle BW, Houghtaling PL, Gillinov AM, Cosgrove DM. Equivalent midterm outcomes after off-pump and on-pump coronary surgery. J Thorac Cardiovasc Surg 2004;127:142–8.
28. Williams ML, Muhlbaier LH, Schroder JN, et al. Risk-adjusted short- and long-term outcomes for on-pump versus off-pump coronary artery bypass surgery. Circulation 2005; 112(9 suppl):I366–70.
29. Hannan EL, Wu C, Smith CR, et al. Off-pump versus on-pump coronary artery bypass graft surgery: differences in short-term outcomes and in long-term mortality and need for subsequent revascularization. Circulation 2007;116:1145–52.
30. Osswald BR, Blackstone EH, Tochtermann U, et al. Does the completeness of revascularization affect early survival after coronary artery bypass grafting in elderly patients? Eur J Cardiothorac Surg 2001;20:120–6.
31. Bell MR, Gersh BJ, Schaff HV, et al. Effect of completeness of revascularization on long-term outcome of patients with three-vessel disease undergoing coronary artery bypass surgery. A report from the Coronary Artery Surgery Study (CASS) Registry. Circulation 1992;86:446–57.
32. Kozower BD, Moon MR, Barner HB, et al. Impact of complete revascularization on long-term survival after coronary artery bypass grafting in octogenarians. Ann Thorac Surg 2005;80:112–7.
33. Synnergren MJ, Ekroth R, Odén A, Rexius H, Wiklund L. Incomplete revascularization reduces survival benefit of coronary artery bypass grafting: role of off-pump surgery. J Thorac Cardiovasc Surg 2008;136:29–36.
34. Aziz A, Lee AM, Pasque MK, et al. Evaluation of revascularization subtypes in octogenarians undergoing coronary artery bypass grafting. Circulation 2009;120(11 suppl):S65–9.
35. Ascione R, Underwood MJ, Lloyd CT, Jeremy JY, Bryan AJ, Angelini GD. Clinical and angiographic outcome of different surgical strategies of bilateral internal mammary artery grafting. Ann Thorac Surg 2001;72:959–65.
36. Gerola LR, Puig LB, Moreira LF, et al. Right internal thoracic artery through the transverse sinus in myocardial revascularization. Ann Thorac Surg 1996;61:1708–13.
37. Pick AW, Orszulak TA, Anderson BJ, Schaff HV. Single versus bilateral internal mammary artery grafts: 10-year outcome analysis. Ann Thorac Surg 1997;64:599–605.
38. Lytle BW, Blackstone EH, Loop FD, et al. Two internal thoracic artery grafts are better than one. J Thorac Cardiovasc Surg 1999;117:855–72.
39. Takagi H, Matsui M, Umemoto T. Lower graft patency after off-pump than on-pump coronary artery bypass grafting: an updated meta-analysis of randomized trials. J Thorac Cardiovasc Surg 2010 Jan 12 [Epub ahead of print].