Prevalence and Impact of Treatment Crossover in Cardiac Surgery Randomized Trials: A Meta-Epidemiologic Study

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***Background*—**Crossover dilutes treatment effect and reduces statistical power of intention-to-treat analysis. We examined incidence and impact on cardiac surgery randomized controlled trial (RCT) outcomes of crossover from experimental to control interventions, or vice versa.

***Methods and Results*—**MEDLINE, EMBASE, and Cochrane Library were searched, and RCTs (≥100 patients) comparing ≥2 adult cardiac surgical interventions were included. Crossover from the initial treatment assignment and relative risks (RRs) for each trial's primary end point and mortality at longest available follow-up were extracted. All RRs were calculated as >1 favored control group and <1 favored experimental arm. Primary outcome was the effect estimate for primary end point of each RCT, and secondary outcome was all-cause mortality; both were appraised as RR at the longest follow-up available. Sixty articles reporting on 47 RCTs (25 440 patients) were identified. Median crossover rate from experimental to control group was 7.0% (first quartile, 2.0%; third quartile, 9.7%), whereas from control to experimental group, the rate was 1.3% (first quartile, 0%; third quartile, 3.6%). RRs for primary end point and mortality were higher in RCTs with higher crossover rate from experimental to control group (RR, 1.01 [95% CI, 0.94–1.07] versus RR, 0.80 [95% CI, 0.66–0.97] and RR, 1.02 [95% CI, 0.95–1.11] versus RR, 0.94 [95% CI, 0.82–1.07], respectively). Crossover from control to experimental group did not alter effect estimates for primary end point or mortality (RR, 0.82 [95% CI, 0.63–1.05] versus RR, 0.95 [95% CI, 0.86–1.04] and RR, 0.88 [95% CI, 0.73–1.07] versus RR, 1.02 [95% CI, 0.95–1.09], respectively).

***Conclusions*—**Crossover from experimental to control group is associated with outcomes of cardiac surgery RCTs. Crossover should be minimized at designing stage and carefully appraised after study completion. **(*J Am Heart Assoc*. 2019;8:e013711. DOI: 10.1161/JAHA.119.013711.)**

Key Words: cardiac surgery • crossover • meta-epidemiologic study • randomized controlled trial • surgery

Randomized controlled trials (RCTs) are considered the gold standard to compare different treatments.[1,2] If duly adhered to, the process of randomization enables the homogeneous distribution of known and unknown risk factors and confounders between treatment arms, thereby allowing for minimization of the bias around the point estimate for a given treatment effect.[2] However, within RCTs, the crossover of subjects from one group to the other dilutes the treatment effect and, even if occurring randomly, reduces the statistical power of the intention-to-treat analysis.[3,4] With high rates of crossover, and even more so when crossover is not random but caused by specific reasons related to the intervention, such as lower confidence or expertise with the experimental therapy, the internal validity of RCTs may be jeopardized and biased effect estimates may ensue, misinforming researchers, clinicians, and patients.[5,6] Crossover is particularly worrisome when

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Accompanying Tables S1 through S5 and Figures S1 through S9 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013711

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Clinical Perspective

What Is New?

- Crossover from experimental to control group is associated with outcomes of cardiac surgery randomized controlled trials.

What Are the Clinical Implications?

- Crossover should be minimized at designing stage and carefully appraised after study completion.

occurring prevalently from one group to the other (1-way crossover). When the prevalent direction is from the experimental to the control arm, crossover may drive the effect estimates toward the null hypothesis, even when the experimental treatment is superior to the control intervention.[7] On the other hand, crossover from control to experimental group may lead to underestimation of the adverse effects associated with a potentially more hazardous experimental treatment.

Surgical RCTs are particularly at risk of crossover issues because of the complex, intricate, and operator-dependent nature of the intervention, the likelihood of a learning curve, the need for specific technical expertise, and the lapse between randomization and intervention.[8–10] For instance, randomization to a novel technique in cardiovascular surgery is typically completed before the operation, whereas the actual feasibility of the procedure can only be fully appraised intraoperatively. Moreover, in surgical RCTs, crossover not only dilutes the potential treatment effect, but may also be a surrogate for lack of confidence or expertise with the novel treatment.[10] This can potentially influence the study results, even beyond the purely statistical effect of crossover.

Given the lack of dedicated investigations on the prevalence and impact of crossover in cardiac surgery, where treatment applicability considerations are arguably among the highest in medicine, the importance and frequency of these interventions for millions of patients worldwide, and the informative, prototypical role of cardiac surgery treatments on medical practice at large, we aimed to systematically evaluate the relationship between crossover rate and outcomes in all RCTs that compared cardiac surgical interventions, by using a meta-epidemiologic approach.[11] Specifically, our main hypothesis was that crossover may unfavorably impact effect estimates, with a high crossover rate diluting clinical effects and, thus, undermining study validity and conclusions.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Design

This meta-epidemiologic study was conducted in keeping with current reviewing practice recommendations,[11] and it is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (Figure S1).[12] The analysis was preregistered on the PROSPERO international database of prospectively registered systematic reviews (identifier: CRD42019123022). There was no individual patient involvement in this study; as such, research ethics board approval was not required.

Search Strategy

A comprehensive search to identify RCTs that compared ≥2 adult cardiac surgical interventions was performed in the following databases: Ovid MEDLINE (all; 1990 to February 2019); Ovid EMBASE (1990 to February 2019); and The Cochrane Library (Wiley). The search strategy included the following terms: "CABG," "off-pump coronary surgery," "on-pump coronary surgery," "arterial grafts," "bilateral internal mammary artery," "bilateral internal thoracic artery," "radial artery," "right gastroepiploic artery," "arterial revascularization," "saphenous vein graft," "mitral valve repair," "mitral valve replacement," "tricuspid valve," "aortic valve replacement," "aortic valve repair," "heart transplant," and "ventricular assist device" (full search strategy available in Table S1). Studies performed on patients with congenital cardiac abnormalities were not included in the search.

Study Selection

Searches across the chosen databases retrieved a total of 10 619 results. After deduplication and removal of nonpertinent articles, 2 independent reviewers (A.D.F., M.D.M.) screened a total of 152 articles. Titles and abstracts were reviewed against predefined inclusion/exclusion criteria. A third independent reviewer (G.F.) confirmed adequacy of studies on the basis of predefined inclusion criteria. Articles were considered for inclusion if they were RCTs with a planned sample size ≥100 patients, published between 1990 and February 2019, comparing ≥2 cardiac surgical interventions in adult patients, and written in English. Studies that compared different devices (not different surgical techniques), surgical versus nonsurgical interventions, and pharmacological or percutaneous treatments were not included. Studies using a noninferiority or equivalence design and for which the primary outcomes or crossover rate was not specified were also excluded. In case of several publications with overlapping study populations, the report that detailed the largest sample size with the longest follow-up available was selected. In case of multiple

publications from the same RCT providing different outcomes, all publications were included. Multiple outcomes from the same trial were included when the sample size was powered for all of them.

The full text of preliminary screened studies was retrieved for a second round of eligibility screening. Disagreements were resolved by the first author (M.G.). Reference lists of the included articles were also searched, and additional studies were included (ie, backward snowballing). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram is shown as Figure S1.

Data Extraction

Two investigators (A.D.F., M.D.M.) performed data extraction independently, and data were later verified by a third investigator (M.G.) for accuracy. The following variables were included: number of studies, number of study reports, total number of comparisons, number of studies with co–primary end points, year of publication, number of multicenter studies, number of centers in multicenter studies, number of off-pump coronary artery bypass graft (CABG) trials, statistical power (%), expected relative risk (RR) reduction (%), sample size, follow-up (months), internal validity, according to Cochrane Risk of Bias Tool, crossover from experimental to control group (%), crossover from control to experimental group (%), total crossover (%), relative crossover (%), main findings, RR for primary end point, and RR for mortality. We also generated a *relative crossover estimate* (defined as crossover from experimental to control group divided by crossover from control to experimental group) and a *total crossover estimate* (defined as the sum of crossover from experimental to control group plus crossover from control to experimental group).

Assessment of the Quality of Individual Studies and the Overall Quality of Evidence

The quality of the included studies was assessed by using the Cochrane Risk of Bias Tool for assessing the internal validity of RCTs.[13]

Outcomes

The primary outcome was the effect estimate for the primary end point of each included RCT, and the secondary outcome was all-cause mortality, both appraised as RR at the longest follow-up available. Whenever possible, RR was recalculated for each study and comparison. When only hazard ratios were reported and RR calculation was unfeasible, hazard ratios were considered as adequate estimators of RR.

Statistical Analysis

Regardless of the way the individual trial was initially reported, for this review, all RRs were calculated as >1 favored the control group and <1 favored the experimental arm.

Continuous variables are reported as median (first quartile; third quartile), and categorical variables are reported as count (%). Exploratory inferential analysis was based on χ^2 or Wilcoxon rank-sum tests. The main inferential analysis was based on random effects pairwise meta-analysis and on meta-regression, using the logarithm of RR (LogRR) as dependent variable, with graphical synthesis by means of forest and L'Abbè plots. Inconsistency was appraised as I^2, τ^2, and χ^2 tests, with between-subgroup heterogeneity tested with an inverse-variance-weighting model. Adjusted R^2 was also used to describe predictive ability. A sensitivity analysis using absolute LogRR (ie, |LogRR|) was also conducted, as it may capture extreme effects better when treatments undergoing comparison may have been defined experimental versus standard inappropriately. In addition, we also conducted an exploratory analysis to identify features independently associated with high crossover rate. Publication bias and small study effects were explored by visual inspection of funnel plots and computing Egger and Begg tests. Effects are reported as point estimates (95% CIs). Computations were performed with Stata 13 (StataCorp, College Station, TX). Studies having a continuous variable as the primary outcome measure were not included in the main analysis.

Results

After searches and selection, 60 reports (accounting for 67 comparisons) from 47 RCTs were identified (25 440 total patients) (Table 1; references of the included RCTs are provided in the supplemental material). Most RCTs focused on off-pump versus on-pump CABG; 5 focused on radial versus saphenous vein grafting; 2 focused on repair versus replacement of the mitral valve; 2 focused on total arterial revascularization versus left internal thoracic artery plus saphenous vein grafting; and the remaining RCTs focused on CABG, mitral valve disease, and aortic valve disease (Table S2). Most studies (n=27 [57.4%]) were limited to 1 or 2 centers. The a priori median expected RR reduction was 29%, the median sample size was 251 subjects, and the median follow-up was 12 months. The internal validity of included studies was variable, with few studies at low risk of bias in all appraised dimensions, and several at high risk (Table S3). Crossover from the experimental to control group occurred in 7.0% (first quartile, 2.0%; third quartile, 9.7%) of patients, whereas crossover from the control to experimental group took place in 1.3% (first quartile, 0%; third quartile, 3.6%) of patients. Inferential estimates of the primary end

point favored the experimental treatment in 13 RCTs and the control group in 4, and were not significantly different in 50 cases. The median RR for primary end point was 0.95 (95% CI, 0.65–1.12), and the median RR for mortality was 0.99 (95% CI, 0.80–1.28).

A meta-epidemiologic analysis that explores the study features associated with higher versus lower than median crossover rate, from experimental to control group, is provided in Table 2. Off-pump CABG trials showed a higher prevalence of crossover from experimental to control group, as did studies on valve surgery, allocating less invasive treatments to the experimental arm and focusing on a mortality or clinical end point, low, moderate, or uncertain internal validity, according to the Cochrane Risk of Bias Tool assessment, and nonsignificant inferential estimates for the trial's primary end point (all $P<0.05$ at χ^2 test). Crossover from control to experimental group was significantly associated with multicenter setting, focus on a clinical end point, and large sample size (all $P<0.05$ at χ^2 test). Accordingly, the RR for primary end point was higher in RCTs with high crossover rate from experimental to control group ($P=0.040$ by meta-regression analysis) (Table 3) (Figure 1),[14–49] with similar findings pertaining to the RR for mortality ($P=0.015$ by meta-regression analysis) (Figure S2). However, no significant associations were found between crossover from control to experimental group and study findings ($P=0.065$ at χ^2 test), nor RR for primary end point ($P=0.726$ at meta-regression analysis) (Figure 2)[14–49] or RR for mortality ($P=0.871$ at meta-regression analysis) (Figure S3).

Another additional important finding of meta-regression analysis was the significant association between the RR for the primary end point ($P=0.038$) and for mortality ($P=0.025$) with off-pump CABG, with effect estimates significantly in favor of the control intervention (ie, on-pump CABG). Other nominally significant associations with the RR for the primary end point or for mortality occurred for the following: rate of crossover from experimental to control group (Figures S4 and S5); CABG trials; and trials allocating more invasive treatments to the experimental arm. Accompanying L'Abbè plots for the association between the rate of crossover from control to experimental group and the RRs for the primary end point and mortality are provided in Figures S6 and S7. Visual inspection highlights the lack of an evident crossover threshold.

Exploratory analysis to identify multivariable predictors of crossover (Table S4) suggested that crossover from experimental to control group was mostly associated with patency as primary end point ($P=0.036$). In addition, meta-regression focusing on *total crossover* rate instead of relative crossover confirmed the overall findings (Table 3), with significant associations found for this composite variable and the RR for the primary end point ($P=0.037$) and for mortality ($P=0.021$). In contrast, *relative crossover* was not significantly associated with significant effect on the RR. Last, sensitivity analysis using |LogRR| (Table S5) showed that CABG trials ($P=0.012$), trials with a mortality end point ($P<0.001$), trials

Table 1. Main Features of Included Studies

Feature	Value, Count (%) or Median (First Quartile; Third Quartile)
Studies	47
Study reports	60
Total no. of comparisons	67
Studies with co–primary end points	8 (17.8)
Year of publication	2009 (2004; 2012)
Multicenter studies	20 (42.6)
No. of centers in multicenter studies	15 (7; 24)
Treatment features	
Coronary artery bypass graft trials	42 (89.4)
Off-pump coronary artery bypass graft trials	27 (57.4)
Valve trials	9 (19.2)
Experimental group more invasive than control group	14 (29.8)
End point features	
Mortality end point	24 (51.1)
Clinical end point	22 (46.8)
Patency end point	13 (27.7)
Statistical power, %	80 (80; 90)
Expected relative risk reduction, %	29 (18; 37)
Sample size	251 (128; 401)
Follow-up, mo	12 (1; 36)
Internal validity according to Cochrane Risk of Bias Tool	
High	8 (11.9)
Moderate or uncertain	48 (71.6)
Low	11 (16.4)
Crossover from experimental to control group, %	7.0 (2.0; 9.7)
Crossover from control to experimental group, %	1.3 (0; 3.6)
Total crossover, %	7.8 (3.0; 10.7)
Relative crossover, %	3.6 (1.0; 19.0)
Main findings	
Favors experimental group	13 (19.4)
Favors control group	4 (6.0)
Nonsignificant	50 (74.6)
Relative risk for primary end point	0.95 (0.65; 1.12)
Relative risk for mortality	0.99 (0.80; 1.28)

Table 2. Inferential Analysis Comparing Higher vs Lower Than Median Crossover Rate

Variable	Value, Count (%) or Median (First Quartile; Third Quartile)		
	High Crossover Rate*	Low Crossover Rate†	*P* Value
From experimental to control group			
Year of publication	2010 (2004; 2014)	2010 (2008; 2012)	0.796
Multicenter studies	20 (58.8)	14 (42.2)	0.179
Treatment features			
Coronary artery bypass graft trials	31 (91.2)	30 (90.9)	0.969
Off-pump coronary artery bypass graft trials	25 (73.5)	14 (42.4)	0.010
Valve trials	3 (8.8)	9 (27.3)	0.049
Experimental group more invasive than control group	7 (20.6)	15 (45.5)	0.030
End point features			
Mortality end point	26 (76.5)	12 (36.4)	0.001
Clinical end point	22 (64.7)	11 (33.3)	0.010
Patency end point	3 (8.8)	13 (39.4)	0.003
Statistical power, %	90 (80; 90)	80 (80; 90)	0.290
Expected relative risk reduction, %	32 (28; 33)	18 (15; 40)	0.227
Sample size	290 (176; 2394)	260 (150; 339)	0.123
Follow-up, mo	12 (1; 24)	15 (1; 35)	0.228
Crossover from control to experimental group, %	1.9 (0; 3.6)	0.9 (0; 3.7)	0.722
Total crossover, %	10.0 (8.7; 13.4)	3.0 (1.0; 5.4)	<0.001
Relative crossover	5.6 (2.3; 85.0)	1.0 (0.3; 10.0)	<0.001
Internal validity according to Cochrane Risk of Bias Tool			
High	1 (2.9)	7 (21.2)	0.003
Moderate or uncertain	23 (67.7)	25 (75.8)	
Low	10 (29.4)	1 (3.0)	
Main findings for primary end point			
Favors experimental group	2 (5.9)	11 (33.3)	0.016
Favors control group	2 (5.9)	2 (6.1)	
Nonsignificant	30 (88.2)	20 (60.6)	
Relative risk for primary end point	1.00 (0.91; 1.22)	0.77 (0.52; 1.00)	0.054
Relative risk for mortality	1.02 (0.93; 1.30)	0.88 (0.61; 1.03)	0.022
From control to experimental group			
Year of publication	2011 (2009; 2014)	2008 (2004; 2011)	0.055
Multicenter studies	24 (70.6)	10 (30.3)	0.001
Treatment features			
Coronary artery bypass graft trials	33 (97.1)	28 (84.9)	0.080
Off-pump coronary artery bypass graft trials	19 (55.9)	20 (60.6)	0.695
Valve trials	4 (11.8)	8 (24.2)	0.183
Experimental group more invasive than control group	13 (38.2)	9 (27.3)	0.339
End point features			
Mortality end point	23 (67.7)	15 (45.5)	0.067
Clinical end point	21 (61.8)	12 (36.4)	0.038

Continued

Table 2. Continued

Variable	Value, Count (%) or Median (First Quartile; Third Quartile)		
	High Crossover Rate*	Low Crossover Rate†	*P* Value
Patency end point	7 (20.6)	9 (27.3)	0.521
Statistical power, %	82 (80; 90)	80 (80; 90)	0.721
Expected relative risk reduction, %	28 (20; 33)	30 (14; 50)	0.926
Sample size	475 (301; 2394)	176 (120; 251)	<0.001
Follow-up, mo	12 (1; 60)	12 (1; 24)	0.275
Internal validity according to Cochrane Risk of Bias Tool			
High	4 (11.8)	4 (12.1)	0.642
Moderate or uncertain	23 (67.7)	25 (75.8)	
Low	7 (20.6)	4 (12.1)	
Crossover from experimental to control group, %	7.0 (3.9; 12.4)	7.4 (1.0; 9.0)	0.269
Total crossover, %	10.0 (8.7; 13.4)	3.0 (1.0; 5.4)	0.074
Relative crossover	1.9 (1.0; 3.4)	16.6 (5.3; 85.0)	<0.001
Main findings for primary end point			
Favors experimental group	3 (8.8)	1 (3.0)	0.065
Favors control group	3 (8.8)	10 (30.3)	
Nonsignificant	28 (82.4)	22 (66.7)	
Relative risk for primary end point	0.98 (0.83; 1.14)	0.78 (0.52; 1.08)	0.468
Relative risk for mortality	1.01 (0.91; 1.28)	0.92 (0.70; 1.29)	0.174

*Higher or equal to the median.
†Lower than the median.

with a clinical end point (*P*=0.044), sample size (*P*=0.006), follow-up (*P*=0.023), study validity (*P*=0.022), crossover from experimental to control group (*P*=0.007), and total crossover (*P*=0.005) were significantly associated with the |LogRR| for the primary end point. Furthermore, year of publication (*P*=0.034), multicenter design (*P*<0.001), sample size (*P*=0.004), study validity (*P*=0.009), and crossover from control to experimental group (*P*=0.021) were significantly associated with the |LogRR| for mortality. Finally, visual inspection of funnel plots showed borderline small study effects/publication bias for the RR of the primary end point and no significant small study effects/publication bias for the RR of mortality (Figures S8 and S9).

Discussion

The optimal approach to personalized medicine and therapeutics entails a complex synthesis of diagnostic and treatment skills. Cardiac surgical management, arguably, appears particularly demanding as surgeons have to master advanced technical requirements while applying evidence-based recommendations. As such, clinical research designed and conducted in this particularly challenging scenario, with uncertain applicability and generalizability, requires careful scrutiny of its strengths and weaknesses. By including all RCTs focusing on cardiac surgical interventions, we hereby provide a comprehensive and updated perspective on the prevalence of crossover from experimental to control group and vice versa in cardiac surgery RCTs, highlighting the detrimental impact of high crossover from experimental to control group in terms of effect dilution for the primary end point and for mortality. We corroborate these findings using a comprehensive estimate of crossover and absolute effect estimates, thus in a more generalistic context.

By definition, crossover dilutes the treatment effect in the intention-to-treat analysis. It has been estimated that, for a fixed sample size and power, the increase of the crossover rate from 0% to 25% may reduce the power of the study from 77% to 57%.[6] In surgical RCTs, things are even more complex, as crossover rate from the experimental to the control group may be to be a marker of a lack of familiarity of the participating surgeons with the (usually new or more complex) surgical procedure performed in the experimental arm. In this case, the association between crossover and outcome may overcome the purely statistical diluting effect of crossover in general and suggests a problem with the deliverability of the procedure. In fact,

Table 3. Meta-Regression Analysis Exploring Potential Moderators of Effect Sizes

Variable	Coefficient (95% CI)	*P* Value	τ^2	Adjusted R^2
Logarithm of the relative risk of the primary end point				
Year of publication	−0.002 (−0.031 to 0.027)	0.904	0.055	0.118
Multicenter studies	−0.091 (−0.366 to 0.183)	0.504	0.054	0.559
Coronary artery bypass graft trials	0.256 (0.015 to 0.497)	0.038	0.040	0.194
Off-pump coronary artery bypass graft trials	0.256 (0.015 to 0.497)	0.038	0.040	0.513
Valve trials	−0.290 (−0.637 to 0.057)	0.099	0.045	0.075
Experimental group more invasive than control group	−0.245 (−0.489 to −0.001)	0.049	0.038	0.239
Mortality end point	0.216 (−0.040 to 0.472)	0.096	0.020	0.595
Clinical end point	0.153 (−0.102 to 0.409)	0.232	0.035	0.284
Patency end point	−0.066 (−0.376 to 0.244)	0.670	0.049	0.003
Statistical power, %	−0.070 (−2.786 to 2.646)	0.958	0.058	0.633
Expected relative risk reduction, %	−0.014 (−0.028 to 0.001)	0.067	0	0.104
Sample size	0.000 (0.000 to 0.000)	0.292	0.047	0.542
Follow-up, mo	0.002 (−0.002 to 0.006)	0.336	0.041	0.532
High internal validity	−0.083 (0.426 to 0.260)	0.625	0.048	0.534
High, moderate, or uncertain validity	−0.076 (−0.408 to 0.256)	0.644	0.054	0.556
Crossover from experimental to control group, %	0.027 (0.001 to 0.053)	0.040	0.025	0.474
Crossover from control to experimental group, %	−0.010 (−0.068 to 0.048)	0.726	0.056	0.556
Total crossover, %	0.027 (0.002 to 0.052)	0.037	0.025	0.469
Relative crossover	−0.001 (−0.007 to 0.004)	0.640	0.052	0.556
Logarithm of the relative risk of mortality				
Year of publication	−0.003 (−0.037 to 0.031)	0.842	0.099	0.488
Multicenter studies	−0.059 (−0.374 to 0.257)	0.710	0.099	0.490
Coronary artery bypass graft trials	0.346 (−0.268 to 0.959)	0.262	0.093	0.013
Off-pump coronary artery bypass graft trials	0.313 (0.041 to 0.585)	0.025	0.062	0.324
Valve trials	−0.284 (−0.703 to 0.134)	0.178	0.092	0.001
Experimental group more invasive than control group	−0.223 (−0.537 to 0.090)	0.157	0.083	0.099
Mortality end point	0.218 (−0.125 to 0.560)	0.207	0.087	0.055
Clinical end point	0.212 (−0.108 to 0.532)	0.188	0.089	0.034
Patency end point	−0.306 (−0.700 to 0.088)	0.125	0.090	0.026
Statistical power, %	−1.945 (−4.607 to 0.716)	0.147	0.076	0.472
Expected relative risk reduction, %	−0.003 (−0.040 to 0.033)	0.824	0.027	0.573
Sample size	0.000 (0.000 to 0.000)	0.519	0.010	0.476
Follow-up, mo	0.002 (−0.003 to 0.007)	0.446	0.099	0.488
High internal validity	−0.405 (−0.834 to 0.025)	0.064	0.079	0.439
High, moderate, or uncertain validity	0.060 (−0.341 to 0.461)	0.764	0.102	0.488
Crossover from experimental to control group, %	0.040 (0.008 to 0.071)	0.015	0.073	0.399
Crossover from control to experimental group, %	0.005 (−0.062 to 0.073)	0.871	0.100	0.086
Total crossover, %	0.037 (0.006 to 0.067)	0.021	0.076	0.405
Relative crossover	−0.001 (−0.006 to 0.005)	0.815	0.097	0.486

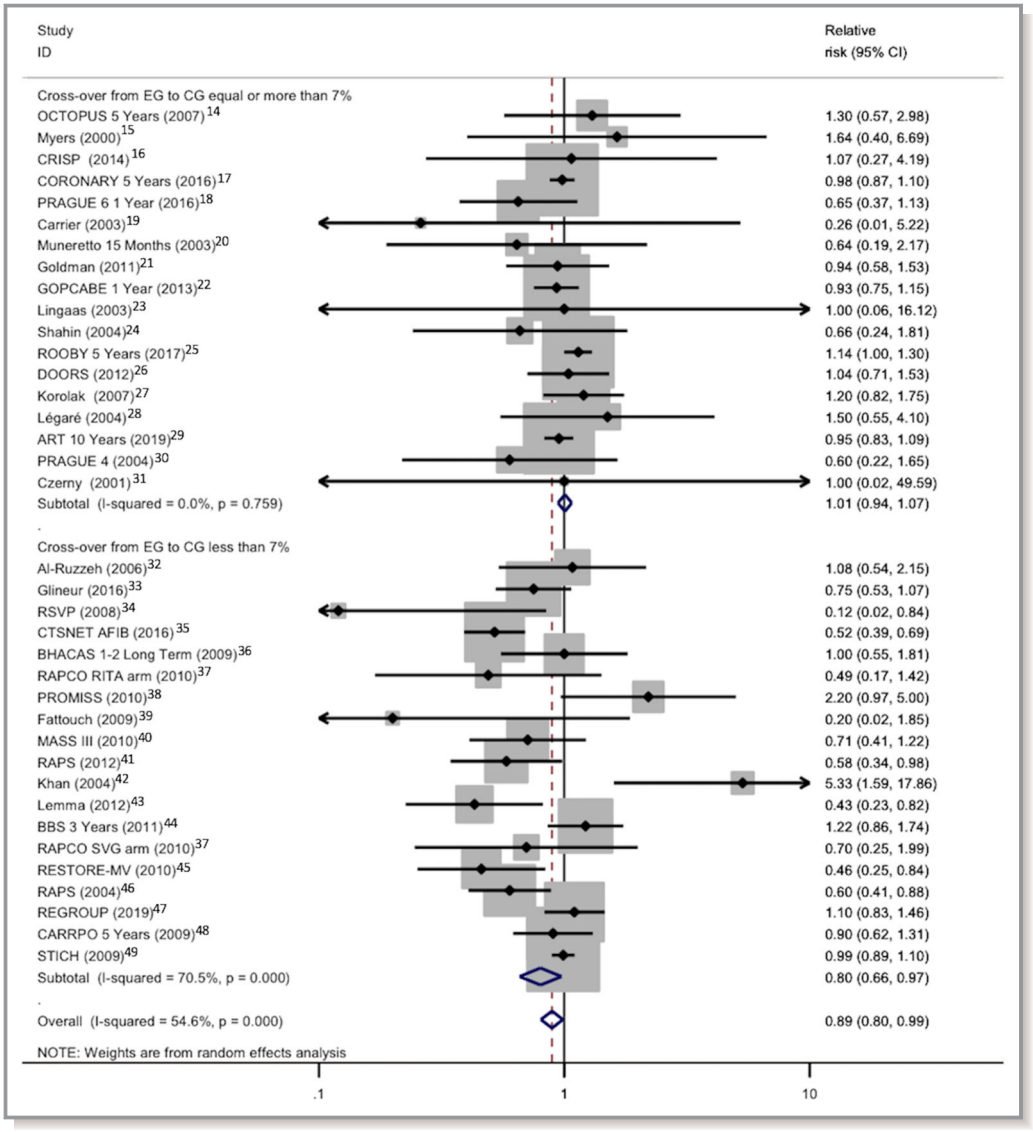


Figure 1. Forest plot for the relative risk of the primary end point, with studies subgrouped and then sorted according to decreasing rate of crossover from experimental group (EG) to control group (CG). All relative risks were calculated as >1 favored the CG and <1 favored the EG. Between-group heterogeneity *P*=0.017. ART, Randomized Trial of Bilateral versus Single Internal-Thoracic-Artery Grafts; BBS, Best Bypass Surgery Trial; BHACAS, Beating Heart Against Cardioplegic Arrest Studies; CARRPO, Copenhagen Arterial Revascularization Randomized Patency and Outcome Trial; CORONARY, CABG Off or On Pump Revascularization Study; CRISP, Coronary artery bypass grafting in high-risk patients randomised to off- or on-pump surgery; CTSNET AFIB, Cardiothoracic Surgical Trials Network - Surgical Ablation of Atrial Fibrillation during Mitral-Valve Surgery; DOORS, Danish On-Pump Versus Off-Pump Randomization Study; GOPCABE, German Off Pump Coronary Artery Bypass in Elderly Study; MASS, Medicine, Angioplasty, or Surgery Study; OCTOPUS, A Comparison of On-Pump and Off-Pump Coronary Bypass Surgery in Low-Risk Patients; PRAGUE 6, Off-Pump Versus On Pump Coronary Artery Bypass Graft Surgery in Patients With EuroSCORE ≥6; PROMISS, Prospective Randomized Comparison of Off-Pump and On-Pump Multivessel Coronary Artery Bypass Surgery; RAPCO SVG, Radial Artery Patency; and Clinical Outcomes trial - saphenous vein graft arm; RAPCO RITA, Radial Artery Patency; and Clinical Outcomes trial - right internal thoracic artery arm; RAPS, radial artery patency study; REGROUP, Randomized Endo-Vein Graft Prospective; RESTORE-MV, Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve; ROOBY, Randomized On/Off Bypass; RSVP, Radial Artery Versus Saphenous Vein Patency Trial; STICH, Surgical Treatment for Ischemic Heart Failure.

crossover has been associated with learning curve, as well as with suboptimal technical and clinical results in surgical RCTs.[5,10]

Crossover rate from off-pump to on-pump CABG was used as a surrogate for surgeon's experience by Gaudino et al.[10] By pooling data from 104 RCTs (20 627 patients), the authors

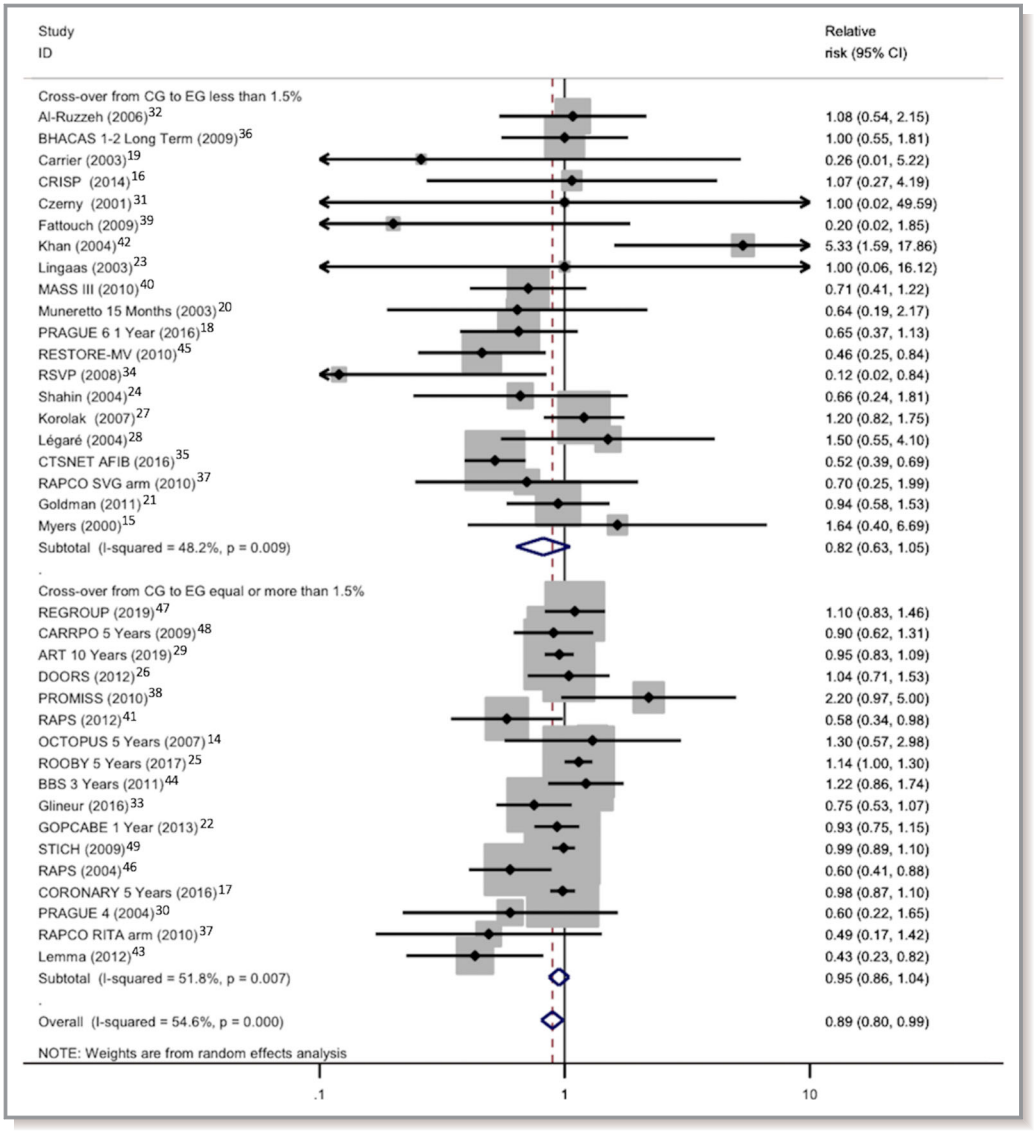


Figure 2. Forest plot for the relative risk of the primary end point, with studies subgrouped and then sorted according to decreasing rate of crossover from control group (CG) to experimental group (EG). All relative risks were calculated as >1 favored the CG and <1 favored the EG. Between-group heterogeneity *P*=0.002. ART, Randomized Trial of Bilateral versus Single Internal-Thoracic-Artery Grafts; BBS, Best Bypass Surgery Trial; BHACAS, Beating Heart Against Cardioplegic Arrest Studies; CARRPO, Copenhagen Arterial Revascularization Randomized Patency and Outcome Trial; CORONARY, CABG Off or On Pump Revascularization Study; CRISP, Coronary artery bypass grafting in high-risk patients randomised to off- or on-pump surgery; CTSNET AFIB, Cardiothoracic Surgical Trials Network - Surgical Ablation of Atrial Fibrillation during Mitral-Valve Surgery; DOORS, Danish On-Pump Versus Off-Pump Randomization Study; GOPCABE, German Off Pump Coronary Artery Bypass in Elderly Study; MASS, Medicine, Angioplasty, or Surgery Study; OCTOPUS, A Comparison of On-Pump and Off-Pump Coronary Bypass Surgery in Low-Risk Patients; PRAGUE 6, Off-Pump Versus On Pump Coronary Artery Bypass Graft Surgery in Patients With EuroSCORE ≥6; PROMISS, Prospective Randomized Comparison of Off-Pump and On-Pump Multl-vessel Coronary Artery Bypass Surgery; RAPCO RITA, Radial Artery Patency; and Clinical Outcomes trial - right internal thoracic artery arm; RAPCO SVG, Radial Artery Patency; and Clinical Outcomes trial - saphenous vein graft arm; RAPS, radial artery patency study; REGROUP, Randomized Endo-Vein Graft Prospective; RESTORE-MV, Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve; ROOBY, Randomized On/Off Bypass; RSVP, Radial Artery Versus Saphenous Vein Patency Trial; STICH, Surgical Treatment for Ischemic Heart Failure.

showed a statistically significant excess risk of late mortality in the off-pump CABG group for studies with a crossover rate ≥10% (incidence rate ratio, 1.30; 95% CI, 1.04–1.62); moreover, at meta-regression, there was a correlation between the proportion of patients who crossed over from off-pump to on-pump CABG and the rate of incomplete

revascularization in the off-pump CABG arm (β=0.0019; *P*=0.03).

In a systematic review of all RCTs comparing minimally invasive surgery with open surgery for gastrointestinal cancer, surgical experience showed an inverse relationship with crossover (β=−2.344; *P*=0.037). At multivariate analysis, a statistically significant correlation between crossover to the open surgery arm and 30-day mortality (β=0.125; *P*=0.033), anastomotic leak rate (β=0.550; *P*=0.004), and early complications (β=1.255; *P*=0.001) was found.[5]

Our analysis cannot shed a conclusive light on the existence of a level of crossover where the results of the intention-to-treat analysis are by definition invalidated. Similarly, we could not find a safety threshold for crossover, below which results of an RCT can be considered bulletproof. Clearly, the complex relation between the crossover, event rate, power, and sample size must be considered on a case-by-case basis. For studies with few events and high crossover rates, major concerns may exist. Pragmatically, we propose that optimal crossover rates should arguably be <5%. The use of entry criteria for surgeons' experience, pretrial training, and close monitoring of crossover rate should be implemented in every surgical RCT to ensure the methodological validity of the trial.

Yet, an RCT does not necessarily correspond to clinical practice, and the design of RCTs is typically based on phase 3 pharmacologic trials. Focusing on the percutaneous coronary intervention versus CABG comparison, for instance, randomization typically occurs after coronary angiography. In addition, it is often the case that percutaneous coronary intervention and CABG are considered complementary, rather than alternative and competing treatments, as in many hybrid revascularization studies. Furthermore, percutaneous coronary intervention after CABG and CABG after percutaneous coronary intervention may also represent disease progression, rather than failure of the initial treatment strategy. Finally, it should be borne in mind that "pure treatment" should not be equated to "intention to treat," and that our work mainly focuses on the features of surgical RCTs according to crossover from pure treatment. Indeed, in selected instances, crossover from pure treatment may actually be correctly mirroring best clinical practice and, thus, be appropriate and justifiable.

Our analysis was also limited to cardiac surgery RCTs where one may argue that the level of technical complexity is usually higher than in other fields of surgery. It is possible that the strength of the association between crossover rate and outcome is different in other surgical or medical specialties. However, our focus on a discipline, such as cardiac surgery, that entails complex organizational and procedural hurdles and involves patients at high risk provides a powerful data set capable of informing on the impact of crossover in surgical trials. Another important limitation of our work is that the included RCTs tested different interventions with different levels of technical complexity and it is likely that the association between crossover and outcome may be different for different procedures. Indeed, statistical heterogeneity was significant in our analysis, as can be expected when appraising studies focusing on heterogeneous end points and interventions. Also, some trial was powered for and reported multiple comparisons, and our model did not adjust for possible interactions. In addition, our work shares all the common limitations of meta-epidemiologic studies, including ecological fallacy, selective reporting, small study effect, and residual confounding. Accordingly, our analysis remains a constructive critique to modern cardiac surgery RCTs, hopefully suitable to inform the conduct, analysis, and interpretation of ongoing and future trials in this field and arguably in other medical and surgical disciplines as well.

In conclusion, we have shown that crossover, particularly from experimental to control group, is associated with outcome, including mortality, in cardiac surgery RCTs. Crossover should be minimized when designing RCTs, and carefully appraised after their completion, to maximize the chance of methodological success and efficient resource use.

Disclosures

Dr Biondi-Zoccai has consulted for Abbott Vascular and Bayer. The remaining authors have no disclosures to report.

References

1. Domanski M, McKinlay S. *Successful Randomized Trials: A Handbook for the 21st Century*. Philadelphia, PA: Lippincott Williams & Wilkins (LWW); 2009.
2. Berger V. *Selection Bias and Covariate Imbalances in Randomized Clinical Trials*. Hoboken, NJ: Wiley; 2007.
3. Peduzzi P, Wittes J, Detre K, Holford T. Analysis as-randomized and the problem of non-adherence: an example from the Veterans Affairs Randomized Trial of Coronary Artery Bypass Surgery. *Stat Med*. 1993;12:1185–1195.
4. Ten Have TR, Normand S-LT, Marcus SM, Brown CH, Lavori P, Duan N. Intent-to-treat vs. non-intent-to-treat analyses under treatment non-adherence in mental health randomized trials. *Psychiatr Ann*. 2008;38:772–783.
5. Garas G, Markar SR, Malietzis G, Ashrafian H, Hanna GB, Zacharakis E, Jiao LR, Argiris A, Darzi A, Athanasiou T. Induced bias due to crossover within randomized controlled trials in surgical oncology: a meta-regression analysis of minimally invasive versus open surgery for the treatment of gastrointestinal cancer. *Ann Surg Oncol*. 2018;25:221–230.
6. Weinstein GS, Levin B. Effect of crossover on the statistical power of randomized studies. *Ann Thorac Surg*. 1989;48:490–495.
7. Balakrishnan N. *Methods and Applications of Statistics in Clinical Trials*. Hoboken, NJ: Wiley; 2014.
8. Cook JA. The challenges faced in the design, conduct and analysis of surgical randomised controlled trials. *Trials*. 2009;10:9.
9. Kodia K, Patel S, Weber MP, Luc JGY, Choi JH, Maynes EJ, Rizvi S-SA, Horan DP, Massey HT, Entwistle JW, Morris RJ, Tchantchaleishvili V. Graft patency after open versus endoscopic saphenous vein harvest in coronary artery bypass grafting surgery: a systematic review and meta-analysis. *Ann Cardiothorac Surg*. 2018;7:586–597.
10. Gaudino M, Benedetto U, Bakaeen F, Rahouma M, Tam DY, Abouarab A, Di Franco A, Leonard J, Elmously A, Puskas JD, Angelini GD, Girardi LN, Fremes SE, Taggart DP. Off- versus on-pump coronary surgery and the effect of follow-up length and surgeons' experience: a meta-analysis. *J Am Heart Assoc*. 2018;7:e010034. DOI: 10.1161/JAHA.118.010034.

11. Biondi-Zoccai G. *Umbrella Reviews: Evidence Synthesis With Overviews of Reviews and Meta-Epidemiologic Studies*. Cham, Switzerland: Springer International; 2016.
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264–269, W64.
13. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JAC; Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
14. van Dijk D, Spoor M, Hijman R, Nathoe HM, Borst C, Jansen EWL, Grobbee DE, de Jaegere PPT, Kalkman CJ; Octopus Study Group. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. *JAMA*. 2007;297:701–708.
15. Myers WO, Berg R, Ray JF, Douglas-Jones JW, Maki HS, Ulmer RH, Chaitman BR, Reinhart RA. All-artery multigraft coronary artery bypass grafting with only internal thoracic arteries possible and safe: a randomized trial. *Surgery*. 2000;128:650–659.
16. Rogers CA, Pike K, Campbell H, Reeves BC, Angelini GD, Gray A, Altman DG, Miller H, Wells S, Taggart DP; CRISP investigators. Coronary artery bypass grafting in high-RISk patients randomised to off- or on-Pump surgery: a randomised controlled trial (the CRISP trial). *Health Technol Assess Winch Engl*. 2014;18:v–xx, 1–157.
17. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Straka Z, Piegas LS, Avezum A, Akar AR, Lanas Zanetti F, Jain AR, Noiseux N, Padmanabhan C, Bahamondes J-C, Novick RJ, Tao L, Olavegogeascoechea PA, Airan B, Sulling T-A, Whitlock RP, Ou Y, Gao P, Pettit S, Yusuf S; CORONARY Investigators. Five-year outcomes after off-pump or on-pump coronary-artery bypass *grafting. N Engl J Med*. 2016;375:2359–2368.
18. Hlavicka J, Straka Z, Jelinek S, Budera P, Vanek T, Maly M, Widimsky P. Off-pump versus on-pump coronary artery bypass grafting surgery in high-risk patients: PRAGUE-6 trial at 30 days and 1 year. *Biomed Pap Med Fac Univ Palacky Olomouc Czechoslov*. 2016;160:263–270.
19. Carrier M, Perrault LP, Jeanmart H, Martineau R, Cartier R, Pagé P. Randomized trial comparing off-pump to on-pump coronary artery bypass grafting in high-risk patients. *Heart Surg Forum*. 2003;6:E89–E92.
20. Muneretto C, Bisleri G, Negri A, Manfredi J, Metra M, Nodari S, Dei Cas L. Off-pump coronary artery bypass surgery technique for total arterial myocardial revascularization: a prospective randomized study. *Ann Thorac Surg*. 2003;76:778–783.
21. Goldman S, Sethi GK, Holman W, Thai H, McFalls E, Ward HB, Kelly RF, Rhenman B, Tobler GH, Bakaeen FG, Huh J, Soltero E, Moursi M, Haime M, Crittenden M, Kasirajan V, Ratliff M, Pett S, Irimpen A, Gunnar W, Thomas D, Fremes S, Moritz T, Reda D, Harrison L, Wagner TH, Wang Y, Planting L, Miller M, Rodriguez Y, Juneman E, Morrison D, Pierce MK, Kreamer S, Shih M-C, Lee K. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. *JAMA*. 2011;305:167–174.
22. Diegeler A, Börgermann J, Kappert U, Breuer M, Böning A, Ursulescu A, Rastan A, Holzhey D, Treede H, Rieß F-C, Veeckmann P, Asfoor A, Reents W, Zacher M, Hilker M; GOPCABE Study Group. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *N Engl J Med*. 2013;368:1189–1198.
23. Lingaas PS, Hol PK, Lundblad R, Rein KA, Tønnesen TI, Svennevig JL, Hauge SN, Vatne K, Fosse E. Clinical and angiographic outcome of coronary surgery with and without cardiopulmonary bypass: a prospective randomized trial. *Heart Surg Forum*. 2004;7:37–41.
24. Shahin GMM, van der Heijden GJMG, Bots ML, Cramer M-J, Jaarsma W, Gadellaa JCA, de la Rivière AB, van Swieten HA. The Carpentier-Edwards Classic and Physio mitral annuloplasty rings: a randomized trial. *Heart Surg Forum*. 2005;8:E389–E394; discussion E394–E395.
25. Shroyer AL, Hattler B, Wagner TH, Collins JF, Baltz JH, Quin JA, Almassi GH, Kozora E, Bakaeen F, Cleveland JC, Bishawi M, Grover FL; Veterans Affairs ROOBY-FS Group. Five-year outcomes after on-pump and off-pump coronary-artery bypass. *N Engl J Med*. 2017;377:623–632.
26. Houlind K, Kjeldsen BJ, Madsen SN, Rasmussen BS, Holme SJ, Nielsen PH, Mortensen PE; DOORS Study Group. On-pump versus off-pump coronary artery bypass surgery in elderly patients: results from the Danish on-pump versus off-pump randomization study. *Circulation*. 2012;125:2431–2439.
27. Karolak W, Hirsch G, Buth K, Légaré J-F. Medium-term outcomes of coronary artery bypass graft surgery on pump versus off pump: results from a randomized controlled trial. *Am Heart J*. 2007;153:689–695.
28. Légaré J-F, Buth KJ, King S, Wood J, Sullivan JA, Friesen CH, Lee J, Stewart K, Hirsch GM. Coronary bypass surgery performed off pump does not result in lower in-hospital morbidity than coronary artery bypass grafting performed on pump. *Circulation*. 2004;109:887–892.
29. Taggart DP, Benedetto U, Gerry S, Altman DG, Gray AM, Lees B, Gaudino M, Zamvar V, Bochenek A, Buxton B, Choong C, Clark S, Deja M, Desai J, Hasan R, Jasinski M, O'Keefe P, Moraes F, Pepper J, Seevanayagam S, Sudarshan C, Trivedi U, Wos S, Puskas J, Flather M; Arterial Revascularization Trial Investigators. Bilateral versus single internal-thoracic-artery grafts at 10 years. *N Engl J Med*. 2019;380:437–446.
30. Straka Z, Widimsky P, Jirasek K, Stros P, Votava J, Vanek T, Brucek P, Kolesar M, Spacek R. Off-pump versus on-pump coronary surgery: final results from a prospective randomized study Prague-4. *Ann Thorac Surg*. 2004;77:789–793.
31. Czerny M, Baumer H, Kilo J, Zuckermann A, Grubhofer G, Chevtchik O, Wolner E, Grimm M. Complete revascularization in coronary artery bypass grafting with and without cardiopulmonary bypass. *Ann Thorac Surg*. 2001;71:165–169.
32. Al-Ruzzeh S, George S, Bustami M, Wray J, Ilsley C, Athanasiou T, Amrani M. Effect of off-pump coronary artery bypass surgery on clinical, angiographic, neurocognitive, and quality of life outcomes: randomised controlled trial. *BMJ*. 2006;332:1365.
33. Glineur D, Boodhwani M, Hanet C, de Kerchove L, Navarra E, Astarci P, Noirhomme P, El Khoury G. Bilateral internal thoracic artery configuration for coronary artery bypass surgery: a prospective randomized trial. *Circ Cardiovasc Interv*. 2016;9:e003518.
34. Collins P, Webb CM, Chong CF, Moat NE; Radial Artery Versus Saphenous Vein Patency (RSVP) Trial Investigators. Radial artery versus saphenous vein patency randomized trial: five-year angiographic follow-up. *Circulation*. 2008;117:2859–2864.
35. Gillinov AM, Gelijns AC, Parides MK, DeRose JJ, Moskowitz AJ, Voisine P, Ailawadi G, Bouchard D, Smith PK, Mack MJ, Acker MA, Mullen JC, Rose EA, Chang HL, Puskas JD, Couderc J-P, Gardner TJ, Varghese R, Horvath KA, Bolling SF, Michler RE, Geller NL, Ascheim DD, Miller MA, Bagiella E, Moquete EG, Williams P, Taddei-Peters WC, O'Gara PT, Blackstone EH, Argenziano M; CTSN Investigators. Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med*. 2015;372:1399–1409.
36. Angelini GD, Culliford L, Smith DK, Hamilton MCK, Murphy GJ, Ascione R, Baumbach A, Reeves BC. 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.
37. Hayward PAR, Gordon IR, Hare DL, Matalanis G, Horrigan ML, Rosalion A, Buxton BF. Comparable patencies of the radial artery and right internal thoracic artery or saphenous vein beyond 5 years: results from the radial artery patency and clinical outcomes trial. *J Thorac Cardiovasc Surg*. 2010;139:60–67.
38. Sousa Uva M, Cavaco S, Oliveira AG, Matias F, Silva C, Mesquita A, Aguiar P, Bau J, Pedro A, Magalhães MP. Early graft patency after off-pump and on-pump coronary bypass surgery: a prospective randomized study. *Eur Heart J*. 2010;31:2492–2499.
39. Fattouch K, Guccione F, Dioguardi P, Sampognaro R, Corrado E, Caruso M, Ruvolo G. Off-pump versus on-pump myocardial revascularization in patients with ST-segment elevation myocardial infarction: a randomized trial. *J Thorac Cardiovasc Surg*. 2009;137:650–657.
40. Hueb W, Lopes NH, Pereira AC, Hueb AC, Soares PR, Favarato D, Vieira RD, Lima EG, Garzillo CL, Paulitch Fda S, César LAM, Gersh BJ, Ramires JAF. Five-year follow-up of a randomized comparison between off-pump and on-pump stable multivessel coronary artery bypass grafting: the MASS III trial. *Circulation*. 2010;122:S48–S52.
41. Deb S, Cohen EA, Singh SK, Une D, Laupacis A, Fremes SE; RAPS Investigators. Radial artery and saphenous vein patency more than 5 years after coronary artery bypass surgery: results from RAPS (Radial Artery Patency Study). *J Am Coll Cardiol*. 2012;60:28–35.
42. Khan NE, De Souza A, Mister R, Flather M, Clague J, Davies S, Collins P, Wang D, Sigwart U, Pepper J. A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. *N Engl J Med*. 2004;350:21–28.
43. Lemma MG, Coscioni E, Tritto FP, Centofanti P, Fondacone C, Salica A, Rossi A, De Santo T, Di Benedetto G, Piazza L, Rinaldi M, De Luca Tupputi Schinosa AL, De Paulis R, Contino M, Genoni M. On-pump versus off-pump coronary artery bypass surgery in high-risk patients: operative results of a prospective randomized trial (on-off study). *J Thorac Cardiovasc Surg*. 2012;143:625–631.
44. Møller CH, Perko MJ, Lund JT, Andersen LW, Kelbæk H, Madsen JK, Winkel P, Gluud C, Steinbrüchel DA. Three-year follow-up in a subset of high-risk patients randomly assigned to off-pump versus on-pump coronary artery bypass surgery: the Best Bypass Surgery Trial. *Heart*. 2011;97:907–913.
45. Grossi EA, Patel N, Woo YJ, Goldberg JD, Schwartz CF, Subramanian V, Feldman T, Bourge R, Baumgartner N, Genco C, Goldman S, Zenati M, Wolfe JA, Mishra YK, Trehan N, Mittal S, Shang S, Mortier TJ, Schweich CJ; RESTOR-MV Study Group. Outcomes of the RESTOR-MV trial (Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve). *J Am Coll Cardiol*. 2010;56:1984–1993.

46. Desai ND, Cohen EA, Naylor CD, Fremes SE. A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. *N Engl J Med*. 2004;351:2302–2309.

47. Zenati MA, Bhatt DL, Bakaeen FG, Stock EM, Biswas K, Gaziano JM, Kelly RF, Tseng EE, Bitondo J, Quin JA, Almassi GH, Haime M, Hattler B, DeMatt E, Scrymgeour A, Huang GD; REGROUP trial investigators. Randomized trial of endoscopic or open vein-graft harvesting for coronary-artery bypass. *N Engl J Med*. 2019;380:132–141.

48. Damgaard S, Wetterslev J, Lund JT, Lilleør NB, Perko MJ, Kelbaek H, Madsen JK, Steinbrüchel DA. One-year results of total arterial revascularization vs. conventional coronary surgery: CARRPO trial. *Eur Heart J*. 2009;30:1005–1011.

49. Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, Hill JA, Menicanti L, Sadowski Z, Desvigne-Nickens P, Rouleau J-L, Lee KL; STICH Hypothesis 2 Investigators. Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med*. 2009;360:1705–1717.

Supplemental Material

Table S1. Full search strategy.

Database: Ovid MEDLINE (In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1990 to February 2019), Ovid EMBASE (1990 to February 2019), and The Cochrane Library (Wiley) for articles published in all languages since 1990. No language restriction enforced.

The specific Ovid MEDLINE strings are the following:
(CABG) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
((off-pump coronary surgery) AND on-pump coronary surgery) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(arterial grafts) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(bilateral internal mammary artery) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(bilateral internal thoracic artery) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(radial artery) AND (CABG) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(right gastroepiploic artery) AND (CABG) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(arterial revascularization) AND (CABG) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(saphenous vein graft) AND (CABG) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(mitral valve repair) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(mitral valve replacement) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(tricuspid valve) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(aortic valve replacement) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(aortic valve repair) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(heart transplant) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])
(ventricular assist device) AND clinical trial [Publication type] AND ("1990"[Date - Publication] : "3000"[Date - Publication])

Table S2. Surgical interventions tested in the included trials. CABG, coronary artery bypass grafting.

Interventions (setting: experimental group vs control group)	**Number of trials**
CABG: bilateral internal thoracic artery vs single internal thoracic artery	1
CABG: bilateral internal thoracic artery Y configuration vs bilateral internal thoracic artery in situ	1
CABG: CABG+Coapsys ventricular reshaping vs CABG+mitral valve repair	1
CABG: CABG+mitral valve repair vs CABG alone	2
CABG: CABG+surgical ventricular reconstruction vs CABG alone	1
CABG: off-pump CABG vs on-pump CABG	27
CABG: radial artery vs right internal thoracic artery	1
CABG: radial artery vs saphenous vein graft	5
CABG: endoscopic vs open vein harvesting	1
CABG: total arterial revascularization vs left internal thoracic artery + saphenous vein graft	2
Mitral valve surgery: loop technique vs mitral leaflet resection	1
Mitral valve surgery: mitral valve repair vs mitral valve replacement	2
Mitral valve surgery: mitral valve surgery+CorCap cardiac support device vs mitral valve surgery alone	1
Mitral valve surgery: mitral valve surgery+surgical atrial fibrillation ablation vs mitral valve surgery alone	1
Mitral valve surgery: Physio Mitral Annuloplasty Ring vs Carpentier–Edwards Classic Annuloplasty Ring	1
Aortic valve surgery: minimally invasive vs full sternotomy aortic valve replacement	1

Table S3. Cochrane Risk of Bias Tool for assessing risk of bias in randomized trials.

		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
Acker	2014	?	?	?	+	+	+	+
ACORN	2006	+	?	?	+	+	+	+
ACORN	2011	+	?	?	+	+	+	+
Al-Ruzzeh	2006	+	+	+	+	+	+	+
ART	2010	+	?	?	+	+	+	+
ART	2016	+	?	?	+	+	+	+
ART	2019	+	?	?	+	+	+	+
BBS 3y	2011	+	?	?	+	+	+	+
BBS early	2010	+	?	?	+	+	+	+
BHACAS 1-2	2002	+	+	+	+	+	+	+
BHACAS 1-2	2009	+	+	+	+	+	+	+
CADENCE-MIS	2015	?	?	?	+	+	+	+
Carrier	2003	+	-	?	?	+	+	+
CARRPO	2009	+	+	?	+	+	+	+
CORONARY 1Y	2012	+	-	-	+	+	+	+
CORONARY 30D	2012	+	-	-	+	+	+	+
CORONARY 5Y	2016	+	-	-	+	+	+	+
CRISP	2014	+	+	+	+	+	+	+
CTSNET AFIB	2016	?	-	-	+	+	+	+
Czerny	2001	?	?	?	?	+	+	+
DOORS	2012	+	-	-	+	+	+	+
Falk	2008	+	+	?	?	+	?	+
Fattouch	2009	+	+	?	+	+	+	+
Glineur	2016	+	+	+	+	+	+	+
Goldman	2011	+	?	?	+	+	+	+
Goldstein	2016	?	?	?	+	+	+	+
GOPCABE	2013	+	?	?	-	+	?	+
JOCRI	2005	+	?	?	?	+	?	?
Khan	2004	?	?	?	+	+	+	+
Korolak	2007	?	?	?	?	+	+	+
Légaré	2004	+	+	+	?	+	+	+
Lemma	2012	+	+	?	?	?	+	+
Lingaas	2003	+	-	+	?	+	+	+
Lingaas	2006	+	-	+	+	+	+	+
MASS III	2010	?	?	?	?	?	+	+
Michaux	2011	+	?	?	+	?	+	+
Michler	2016	?	?	?	?	+	+	+
Muneretto	2003	?	?	?	?	?	+	?
Myers	2000	?	+	+	+	+	+	+
OCTOPUS 1Y	2003	+	?	?	+	+	+	+

OCTOPUS 30-d	2001	?	-	-	+	+	?	+
OCTOPUS 5-y	2007	+	?	?	+	+	+	+
Pegg	2008	?	?	?	+	+	+	+
PRAGUE 4	2004	?	+	?	?	+	?	+
PRAGUE 6	2016	+	+	?	?	+	+	+
PROMISS	2010	+	+	+	+	+	+	+
RAPCO	2010	?	?	?	?	+	+	?
RAPS	2012	+	+	+	+	+	+	+
RAPS	2004	+	+	+	+	+	+	+
REGROUP	2019	+	?	?	+	+	+	+
RESTORE-MV	2010	?	?	?	?	+	+	+
ROOBY 30d/1y	2009	+	?	+	+	+	+	+
ROOBY 5y	2017	+	?	+	+	+	+	+
RSVP	2008	+	+	?	?	+	?	+
Shahin	2004	-	-	?	?	+	?	+
SMART	2004	+	?	?	+	+	+	+
Smith	2014	?	?	?	+	+	+	+
STAND-In-Y	2009	+	?	?	?	+	+	+
STICH	2009	?	-	-	-	+	?	+
Yu	2014	+	+	+	?	+	+	+
				+	Low Risk			
				?	Uncertain			
				-	High Risk			

Table S4. Exploratory analysis for multivariable predictors of high crossover (i.e. higher or equal to the median).*

	Coefficient (95% CI)	P
Crossover from experimental to control group		
Off-pump coronary artery bypass graft trials	3.839 (0.567; 26.015)	0.168
Patency endpoint	0.149 (0.025; 0.887)	0.036
Crossover from control to experimental group		
Follow-up (months)	1.019 (0.992; 1.048)	0.165

*based on stepwise forward logistic regression weighting for sample size (p>0.20 for removal). CI=confidence interval.

Table S5. Meta-regression analysis exploring potential moderators of absolute effect sizes.

	Coefficient (95% CI)	P	Tau-squared	Adjusted R-squared
Absolute of the logarithm of the relative risk of the primary endpoint				
Year of publication	-0.017 (-0.039; 0.005)	0.132	0.027	0.006
Multicenter studies	-0.132 (-0.343; 0.079)	0.212	0.024	0.118
Coronary artery bypass graft trials	-0.461 (-0.812; -0.109)	0.012	0.010	0.629
Off-pump coronary artery bypass graft trials	-0.056 (-0.262; 0.151)	0.588	0.029	0.743
Valve trials	0.115 (-0.168; 0.398)	0.414	0.030	0.116
Experimental group more invasive than control group	0.042 (-0.169; 0.252)	0.690	0.029	0.089
Mortality endpoint	-0.361 (-0.533; -0.189)	<0.001	0.001	0.975
Clinical endpoint	-0.203 (-0.400; -0.006)	0.044	0.020	0.248
Patency endpoint	0.206 (-0.031; 0.444)	0.086	0.020	0.272
Statistical power (%)	-1.057 (-2.986; 0.872)	0.271	0.029	0.863
Expected relative risk reduction (%)	0.014 (-0.001; 0.028)	0.058	0	0
Sample size	-0.000 (-0.001; 0.000)	0.006	0.016	0.415
Follow-up (months)	-0.003 (-0.006; -0.001)	0.023	0.016	0.247
High internal validity	0.150 (-0.118; 0.417)	0.264	0.022	0.184
High, moderate or uncertain validity	0.236 (0.036; 0.436)	0.022	0.016	0.392
Crossover from experimental to control group (%)	-0.029 (-0.049; -0.008)	0.007	0.015	0.429
Crossover from control to experimental group (%)	-0.025 (-0.067; 0.016)	0.226	0.021	0.213
Total crossover (%)	-0.029 (-0.048; -0.009)	0.005	0.015	0.473
Relative crossover	0.002 (-0.003; 0.006)	0.396	0.026	0.021
Absolute of the logarithm of the relative risk of mortality				
Year of publication	-0.025 (-0.048; -0.002)	0.034	0.022	0.128
Multicenter studies	-0.383 (-0.552; -0.214)	<0.001	0.003	0.865
Coronary artery bypass graft trials	-0.034 (-0.460; 0.391)	0.871	0.028	0.093
Off-pump coronary artery bypass graft trials	0.072 (-0.138; 0.281)	0.494	0.026	0.484
Valve trials	-0.091 (-0.362; 0.179)	0.499	0.026	0.030
Experimental group more invasive than control group	-0.093 (-0.307; 0.120)	0.382	0.025	0.002
Mortality endpoint	-0.078 (-0.331; 0.174)	0.535	0.025	0.012
Clinical endpoint	0.010 (-0.219; 0.240)	0.927	0.028	0.101
Patency endpoint	0.109 (-0.189; 0.407)	0.463	0.024	0.030
Statistical power (%)	-1.289 (-3.132; 0.554)	0.164	0.024	0.025
Expected relative risk reduction (%)	0.001 (-0.027; 0.028)	0.940	0	0
Sample size	-0.001 (-0.001; 0)	0.004	0.016	0.394

Follow-up (months)	-0.002 (-0.005; 0.001)	0.155	0.023	0.974
High internal validity	0.116 (-0.222; 0.454)	0.493	0.025	0.018
High, moderate or uncertain validity	0.250 (0.066; 0.434)	0.009	0.012	0.515
Crossover from experimental to control group (%)	-0.011 (-0.035; 0.012)	0.335	0.025	0.011
Crossover from control to experimental group (%)	-0.045 (-0.083; -0.007)	0.021	0.012	0.508
Total crossover (%)	-0.012 (-0.035; 0.010)	0.266	0.024	0.047
Relative crossover	0.002 (-0.002; 0.007)	0.300	0.022	0.122

CI=confidence interval. NC=not computable.

Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

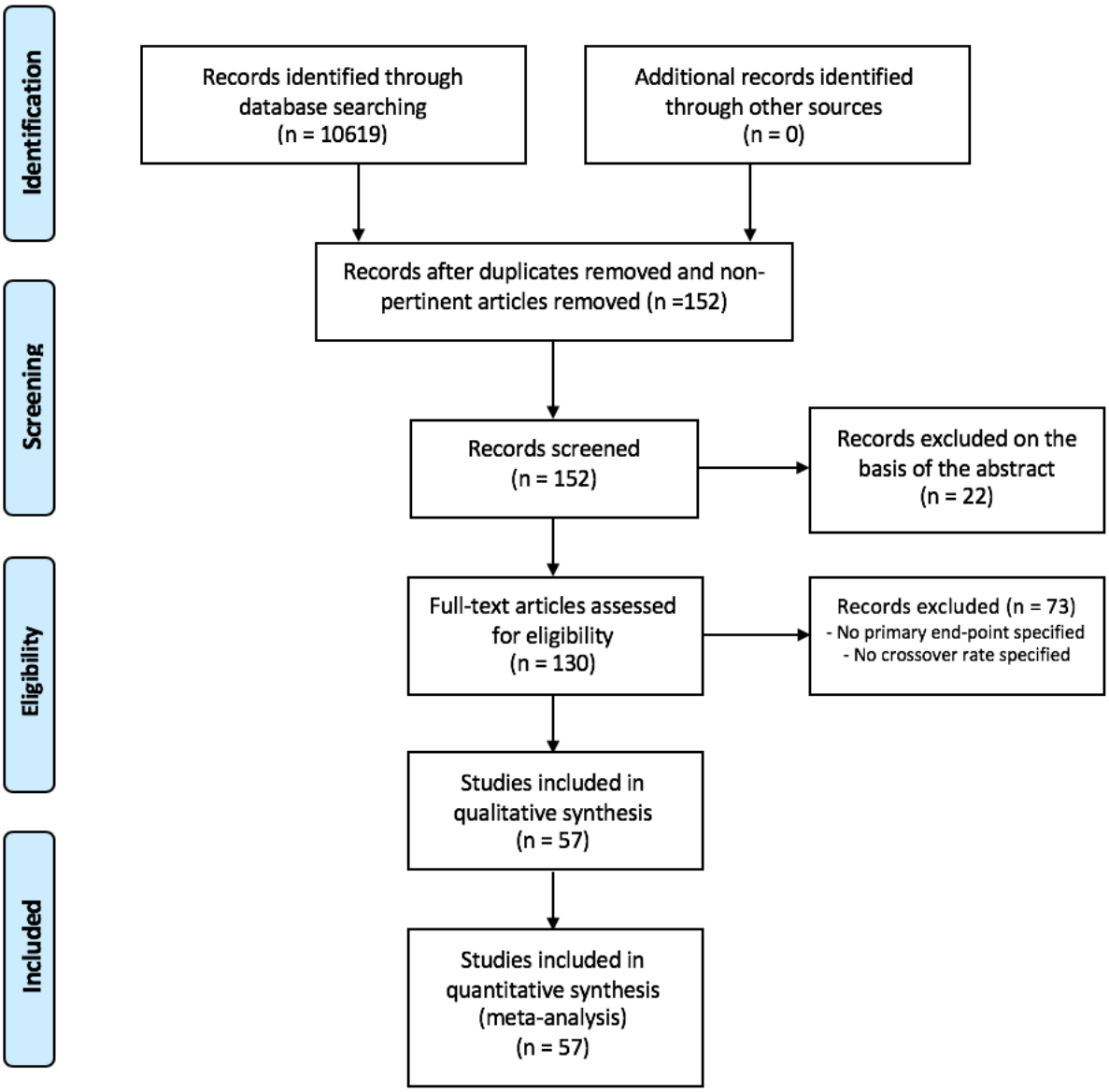
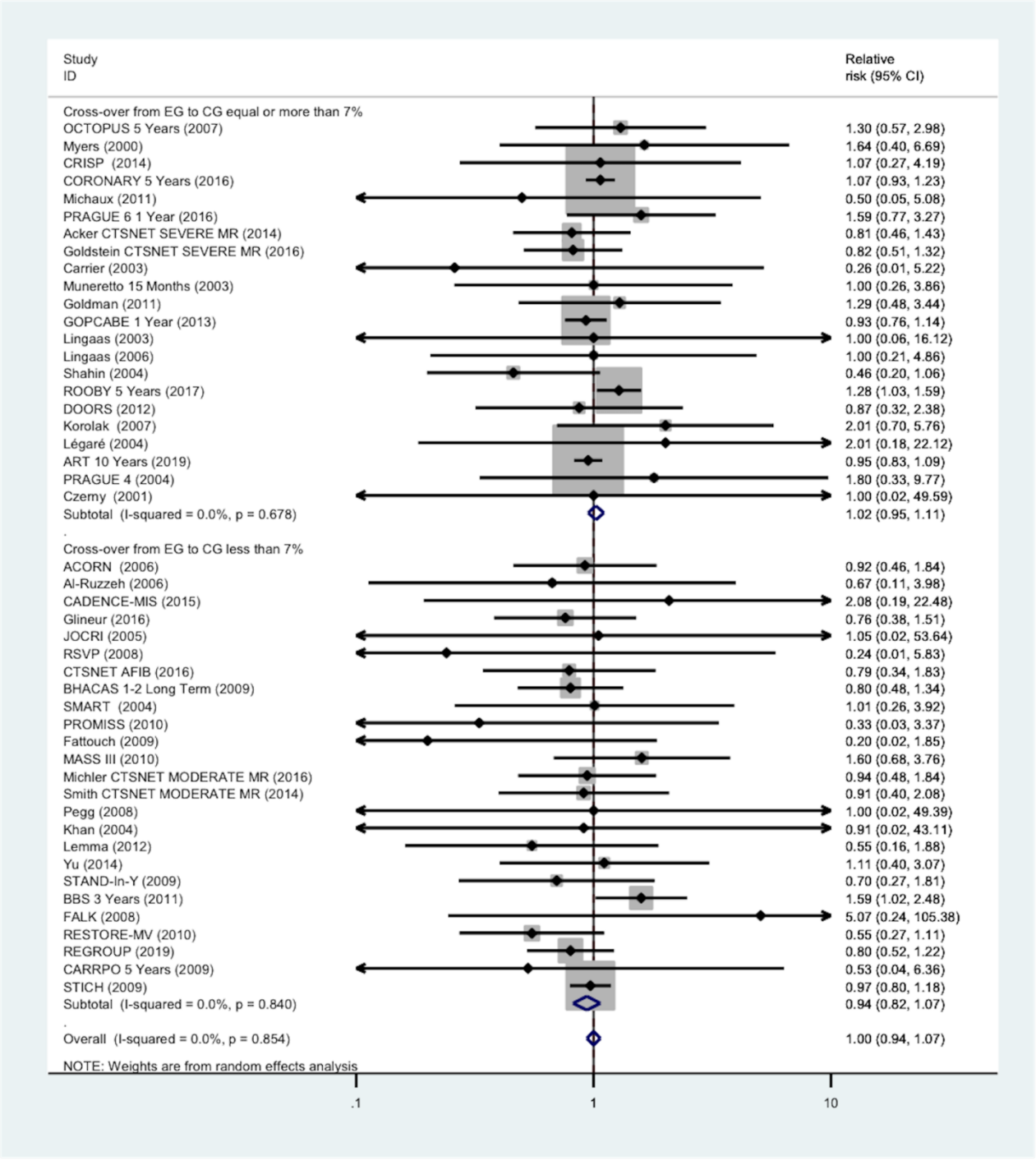
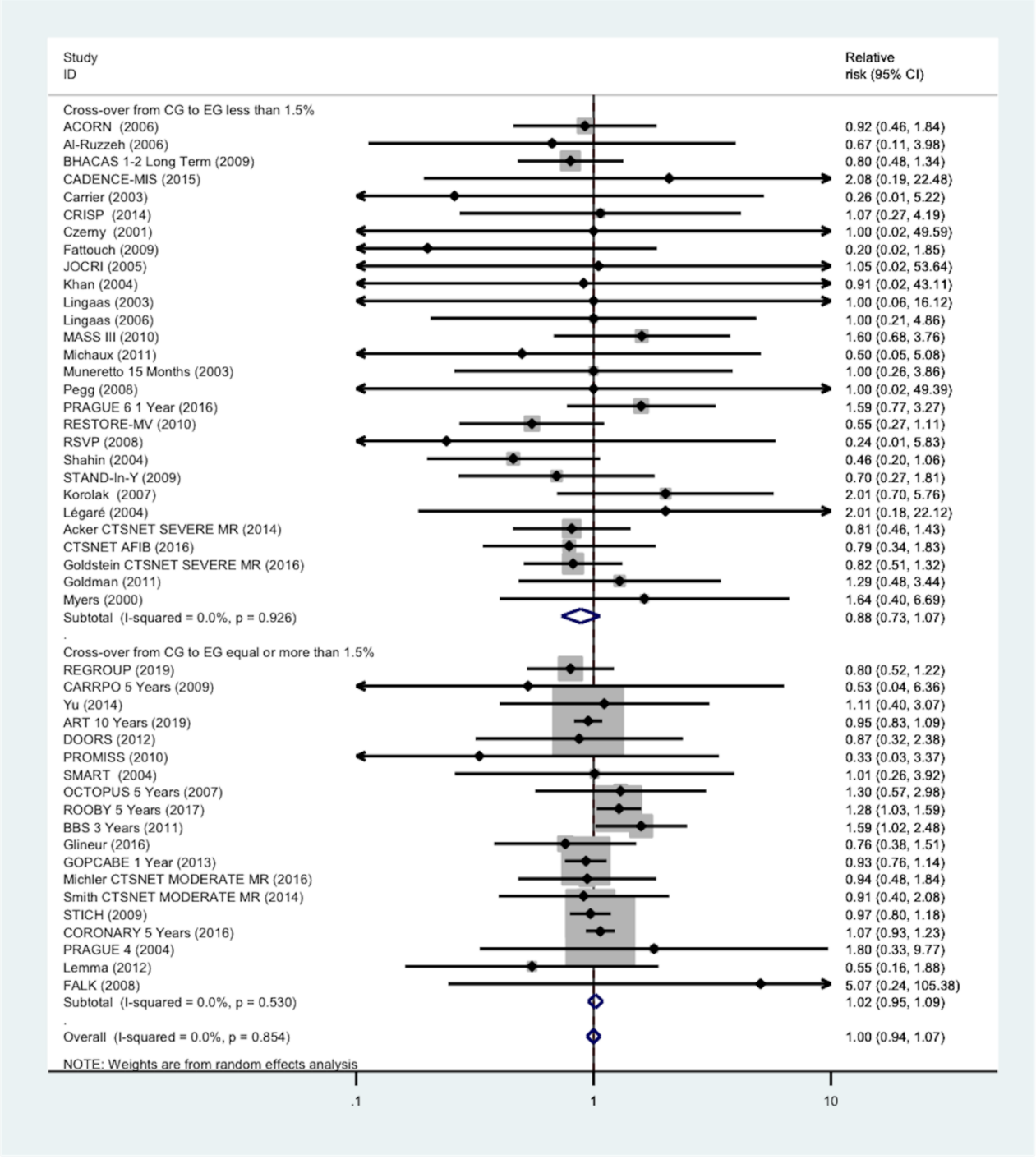


Figure S2. Forest plot for the relative risk of mortality, with studies subgrouped and then sorted according to decreasing rate of crossover from experimental group (EG) to control group (CG).



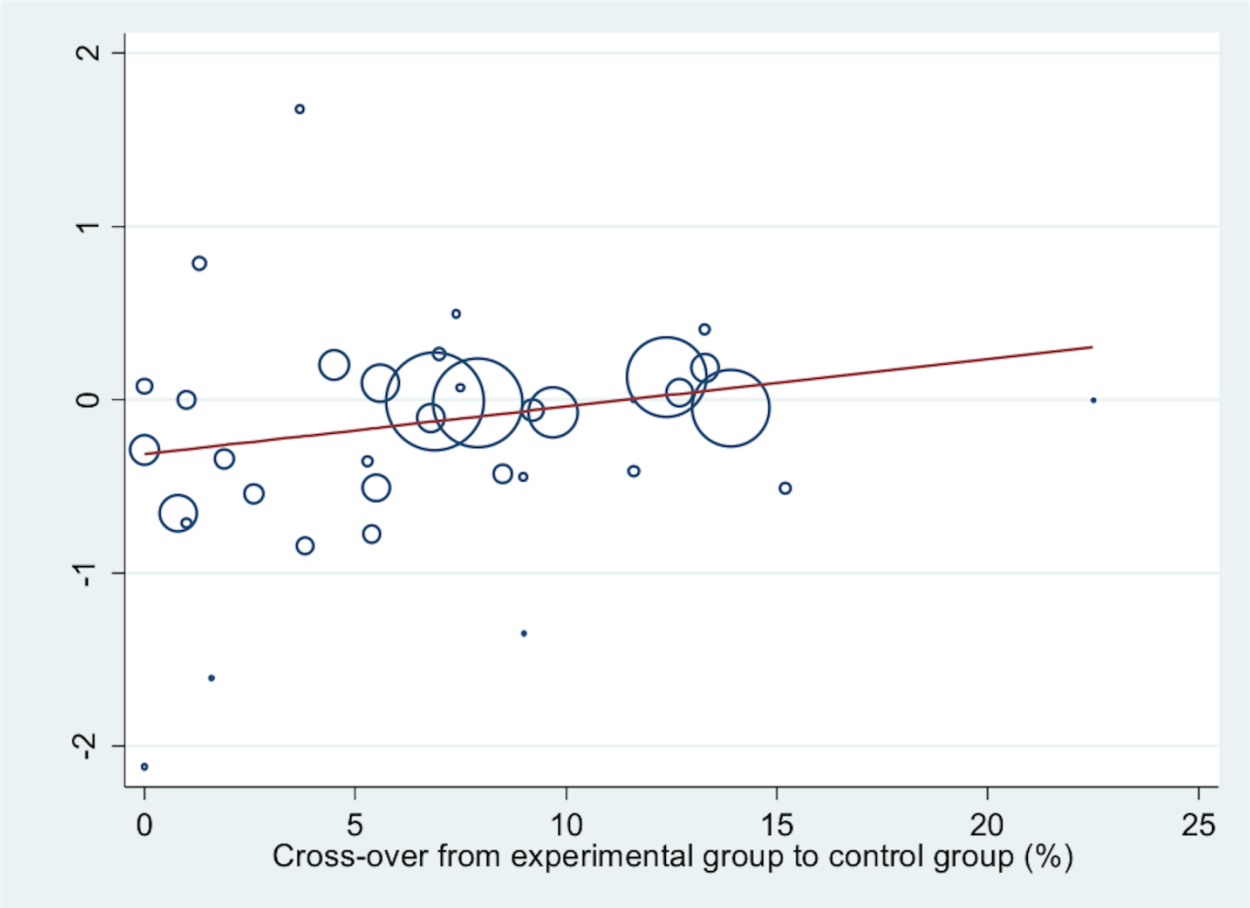
All relative risks were calculated as >1 favored the CG, and <1 favored the EG. Between-group heterogeneity p=0.252. CI=confidence interval.

Figure S3. Forest plot for the relative risk of mortality, with studies subgrouped and then sorted according to decreasing rate of crossover from control group (CG) to experimental group (EG).



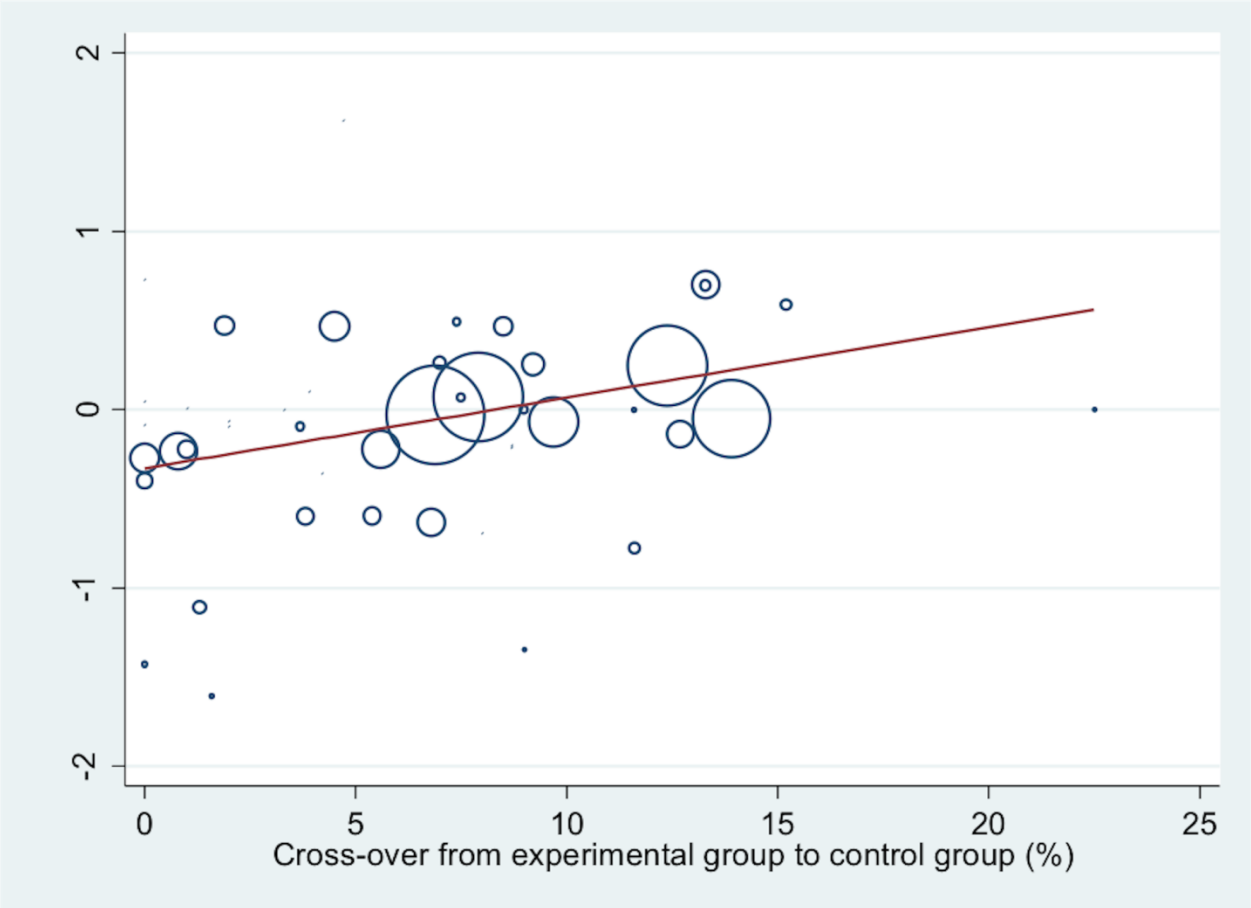
All relative risks were calculated as >1 favored the CG, and <1 favored the EG. Between-group heterogeneity p=0.164. CI=confidence interval.

Figure S4. L'Abbè plot for the association between crossover rate from experimental to control group and logarithm of the relative risk of the primary endpoint.



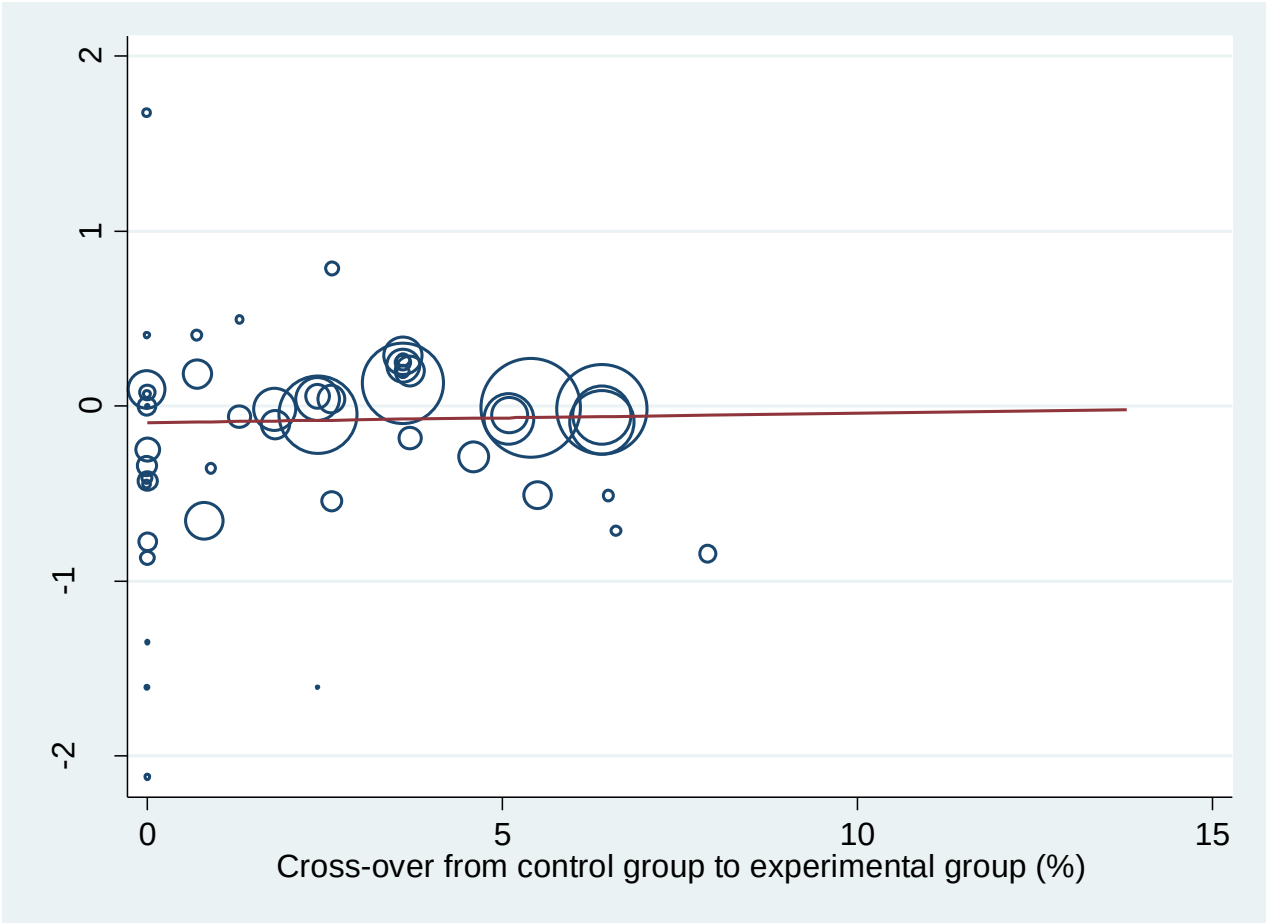
Meta-regression coefficient=0.027 (95% confidence interval: 0.001; 0.053), p=0.040. Tau-squared=0.025. Adjusted R-squared=0.482.

Figure S5. L'Abbè plot for the association between crossover rate from experimental to control group and logarithm of the relative risk of mortality.



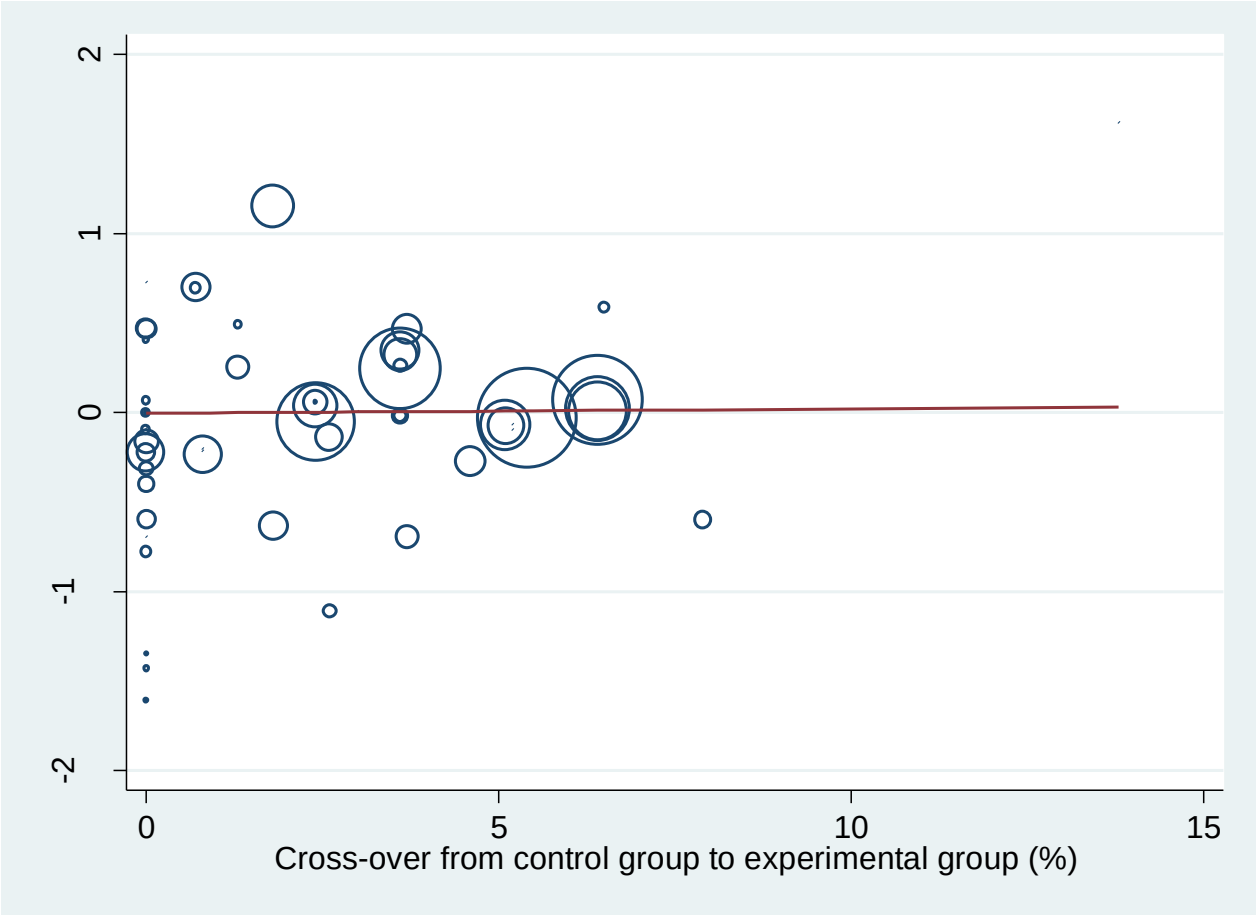
Meta-regression coefficient=0.040 (95% confidence interval: 0.008; 0.071), p=0.015. Tau-squared=0.073. Adjusted R-squared=0.207.

Figure S6. L'Abbè plot for the association between cross-over rate from control to experimental group and logarithm of the relative risk of the primary endpoint.



Meta-regression coefficient=-0.005 (95% confidence interval: -0.036; 0.046), p=0.798. Tau-squared=0.030. Adjusted R-squared=0.078.

Figure S7. L'Abbè plot for the association between cross-over rate from control to experimental group and logarithm of the relative risk of mortality.



Meta-regression coefficient=0.002 (95% confidence interval: -0.058; 0.062), p=0.935. Tau-squared=0.126. Adjusted R-squared=0.040.

Figure S8. Funnel plot showing borderline small study effects/publication bias for the relative risk of the primary endpoint (p=0.090 at Egger test, p=0.360 at Begg test).

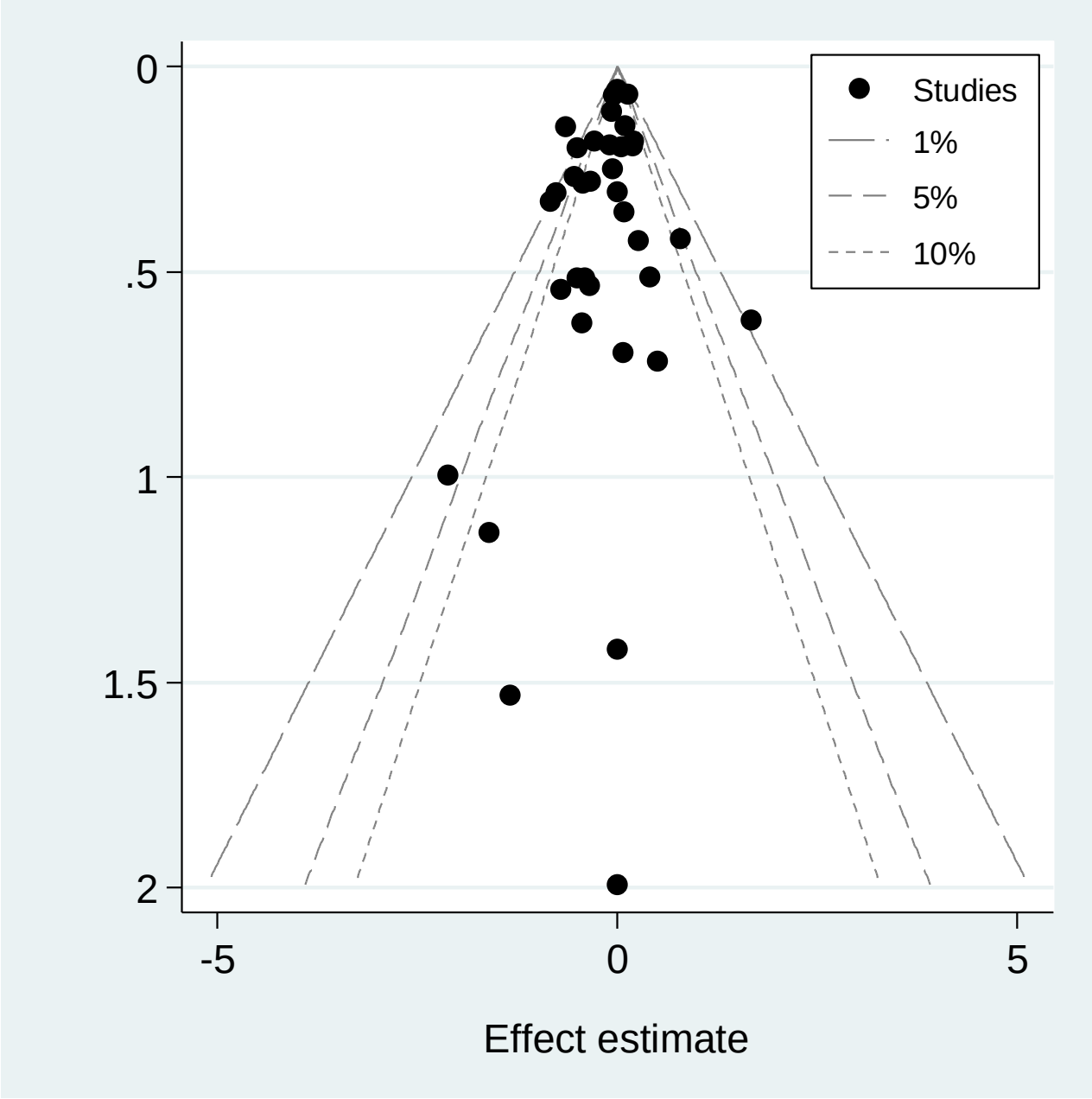
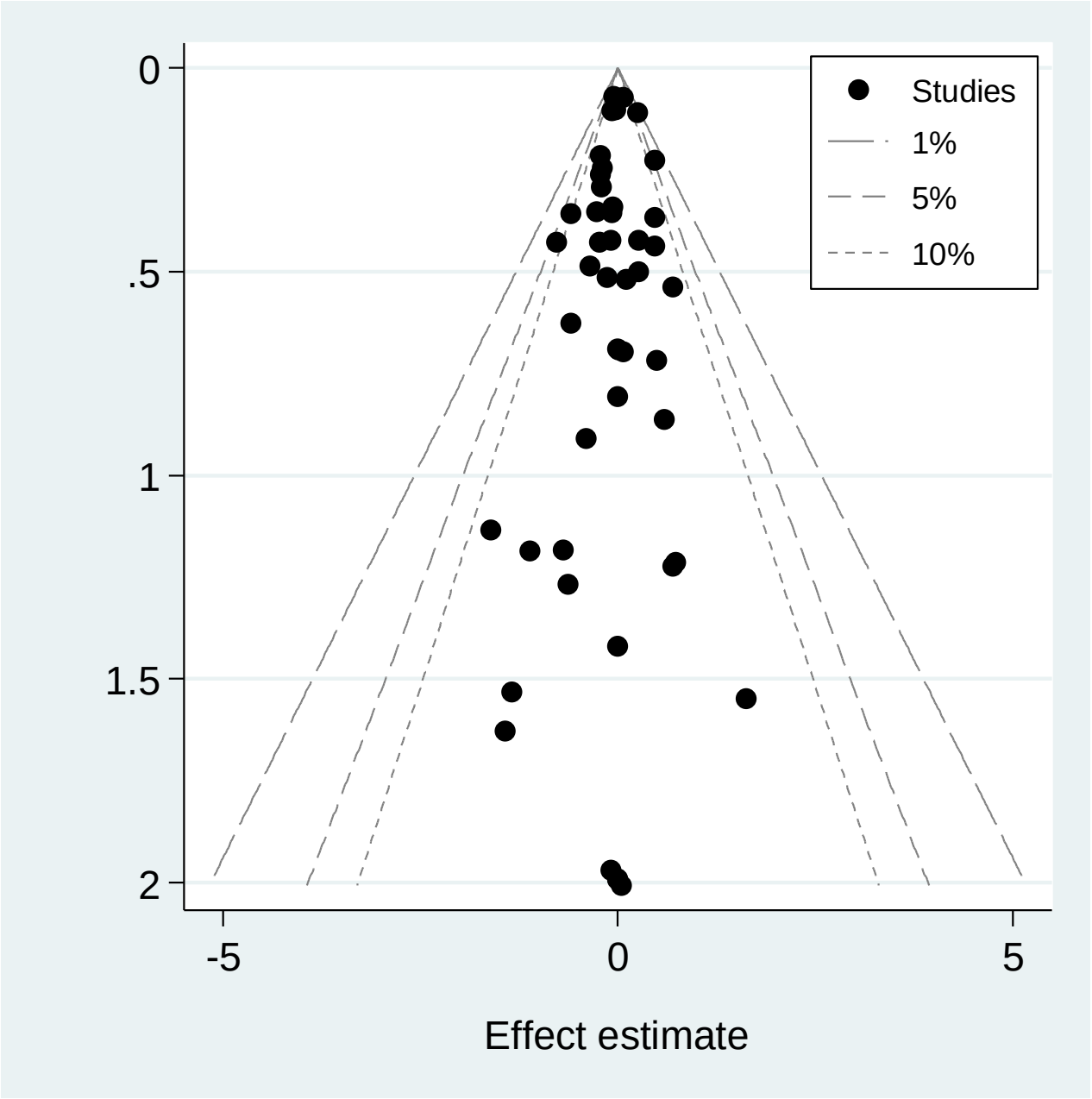


Figure S9. Funnel plot showing no significant small study effects/publication bias for the relative risk of mortality (p=0.328 at Egger test, p=0.492 at Begg test).



Supplemental References:

1. Acker MA, Bolling S, Shemin R, Kirklin J, Oh JK, Mann DL, Jessup M, Sabbah HN, Starling RC, Kubo SH, Acorn Trial Principal Investigators and Study Coordinators. Mitral valve surgery in heart failure: insights from the Acorn Clinical Trial. *J Thorac Cardiovasc Surg*. 2006;132:568–577, 577.e1–4.

2. Acker MA, Jessup M, Bolling SF, Oh J, Starling RC, Mann DL, Sabbah HN, Shemin R, Kirklin J, Kubo SH. Mitral valve repair in heart failure: five-year follow-up from the mitral valve replacement stratum of the Acorn randomized trial. *J Thorac Cardiovasc Surg*. 2011;142:569–574, 574.e1.

3. Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, Smith PK, Hung JW, Blackstone EH, Puskas JD, Argenziano M, Gammie JS, Mack M, Ascheim DD, Bagiella E, Moquete EG, Ferguson TB, Horvath KA, Geller NL, Miller MA, Woo YJ, D'Alessandro DA, Ailawadi G, Dagenais F, Gardner TJ, O'Gara PT, Michler RE, Kron IL, CTSN. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med*. 2014;370:23–32.

4. Al-Ruzzeh S, George S, Bustami M, Wray J, Ilsley C, Athanasiou T, Amrani M. Effect of off-pump coronary artery bypass surgery on clinical, angiographic, neurocognitive, and quality of life outcomes: randomised controlled trial. *BMJ*. 2006;332:1365.

5. Angelini GD, Culliford L, Smith DK, Hamilton MCK, Murphy GJ, Ascione R, Baumbach A, Reeves BC. 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.

6. 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;359:1194–1199.

7. Borger MA, Moustafine V, Conradi L, Knosalla C, Richter M, Merk DR, Doenst T, Hammerschmidt R, Treede H, Dohmen P, Strauch JT. A randomized multicenter trial of minimally invasive rapid deployment versus conventional full sternotomy aortic valve replacement. *Ann Thorac Surg*. 2015;99:17–25.

8. Carrier M, Perrault LP, Jeanmart H, Martineau R, Cartier R, Pagé P. Randomized trial comparing off-pump to on-pump coronary artery bypass grafting in high-risk patients. *Heart Surg Forum*. 2003;6:E89-92.

9. Collins P, Webb CM, Chong CF, Moat NE, Radial Artery Versus Saphenous Vein Patency (RSVP) Trial Investigators. Radial artery versus saphenous vein patency randomized trial: five-year angiographic follow-up. *Circulation*. 2008;117:2859–2864.

10. Czerny M, Baumer H, Kilo J, Zuckermann A, Grubhofer G, Chevtchik O, Wolner E, Grimm M. Complete revascularization in coronary artery bypass grafting with and without cardiopulmonary bypass. *Ann Thorac Surg*. 2001;71:165–169.

11. Damgaard S, Wetterslev J, Lund JT, Lilleør NB, Perko MJ, Kelbaek H, Madsen JK, Steinbrüchel DA. One-year results of total arterial revascularization vs. conventional coronary surgery: CARRPO trial. *Eur Heart J*. 2009;30:1005–1011.

12. Deb S, Cohen EA, Singh SK, Une D, Laupacis A, Fremes SE, RAPS Investigators. Radial artery and saphenous vein patency more than 5 years after coronary artery bypass surgery: results from RAPS (Radial Artery Patency Study). *J Am Coll Cardiol*. 2012;60:28–35.

13. Desai ND, Cohen EA, Naylor CD, Fremes SE. A Randomized Comparison of Radial-Artery and Saphenous-Vein Coronary Bypass Grafts. *N Engl J Med*. 2004;351:2302–2309.

14. Diegeler A, Börgermann J, Kappert U, Breuer M, Böning A, Ursulescu A, Rastan A, Holzhey D, Treede H, Rieß F-C, Veeckmann P, Asfoor A, Reents W, Zacher M, Hilker M, GOPCABE Study Group. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *N Engl J Med*. 2013;368:1189–1198.

15. van Dijk D, Nierich AP, Jansen EWL, Nathoe HM, Suyker WJL, Diephuis JC, Boven van W-J, Borst C, Buskens E, Grobbee DE, Medina de EOR, Jaegere de PPT. Early Outcome After Off-Pump Versus On-Pump Coronary Bypass Surgery: Results From a Randomized Study. *Circulation*. 2001;104:1761–1766.

16. van Dijk D, Spoor M, Hijman R, Nathoe HM, Borst C, Jansen EWL, Grobbee DE, de Jaegere PPT, Kalkman CJ, Octopus Study Group. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. *JAMA*. 2007;297:701–708.

17. Falk V, Seeburger J, Czesla M, Borger MA, Willige J, Kuntze T, Doll N, Borger F, Perrier P, Mohr FW. How does the use of polytetrafluoroethylene neochordae for posterior mitral valve prolapse (loop technique) compare with leaflet resection? A prospective randomized trial. *J Thorac Cardiovasc Surg*. 2008;136:1205; discussion 1205-1206.

18. Fattouch K, Guccione F, Dioguardi P, Sampognaro R, Corrado E, Caruso M, Ruvolo G. Off-pump versus on-pump myocardial revascularization in patients with ST-segment elevation myocardial infarction: A randomized trial. *J Thorac Cardiovasc Surg*. 2009;137:650–657.

19. Gillinov AM, Gelijns AC, Parides MK, DeRose JJ, Moskowitz AJ, Voisine P, Ailawadi G, Bouchard D, Smith PK, Mack MJ, Acker MA, Mullen JC, Rose EA, Chang HL, Puskas JD, Couderc J-P, Gardner TJ, Varghese R, Horvath KA, Bolling SF, Michler RE, Geller NL, Ascheim DD, Miller MA, Bagiella E, Moquete EG, Williams P, Taddei-Peters WC, O'Gara PT, Blackstone EH, Argenziano M, CTSN Investigators. Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med*. 2015;372:1399–1409.

20. Glineur D, Boodhwani M, Hanet C, de Kerchove L, Navarra E, Astarci P, Noirhomme P, El Khoury G. Bilateral Internal Thoracic Artery Configuration for Coronary Artery Bypass Surgery: A Prospective Randomized Trial. *Circ Cardiovasc Interv*. 2016;9.

21. Goldman S, Sethi GK, Holman W, Thai H, McFalls E, Ward HB, Kelly RF, Rhenman B, Tobler GH, Bakaeen FG, Huh J, Soltero E, Moursi M, Haime M, Crittenden M, Kasirajan V, Ratliff M, Pett S, Irimpen A, Gunnar W, Thomas D, Fremes S, Moritz T, Reda D, Harrison L, Wagner TH, Wang Y, Planting L, Miller M, Rodriguez Y, Juneman E, Morrison D, Pierce MK, Kreamer S, Shih M-C, Lee K. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. *JAMA*. 2011;305:167–174.

22. Goldstein D, Moskowitz AJ, Gelijns AC, Ailawadi G, Parides MK, Perrault LP, Hung JW, Voisine P, Dagenais F, Gillinov AM, Thourani V, Argenziano M, Gammie JS, Mack M, Demers P, Atluri P, Rose EA, O'Sullivan K, Williams DL, Bagiella E, Michler RE, Weisel RD, Miller MA, Geller NL, Taddei-Peters WC, Smith PK, Moquete E, Overbey JR, Kron IL,

O'Gara PT, Acker MA, CTSN. Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation. *N Engl J Med*. 2016;374:344–353.

23. Grossi EA, Patel N, Woo YJ, Goldberg JD, Schwartz CF, Subramanian V, Feldman T, Bourge R, Baumgartner N, Genco C, Goldman S, Zenati M, Wolfe JA, Mishra YK, Trehan N, Mittal S, Shang S, Mortier TJ, Schweich CJ, RESTOR-MV Study Group. Outcomes of the RESTOR-MV Trial (Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve). *J Am Coll Cardiol*. 2010;56:1984–1993.

24. Hayward PAR, Gordon IR, Hare DL, Matalanis G, Horrigan ML, Rosalion A, Buxton BF. Comparable patencies of the radial artery and right internal thoracic artery or saphenous vein beyond 5 years: Results from the Radial Artery Patency and Clinical Outcomes trial. *J Thorac Cardiovasc Surg*. 2010;139:60–67.

25. Hlavicka J, Straka Z, Jelinek S, Budera P, Vanek T, Maly M, Widimsky P. Off-pump versus on-pump coronary artery bypass grafting surgery in high-risk patients: PRAGUE-6 trial at 30 days and 1 year. *Biomed Pap Med Fac Univ Palacky Olomouc Czechoslov*. 2016;160:263–270.

26. Houlind K, Kjeldsen BJ, Madsen SN, Rasmussen BS, Holme SJ, Nielsen PH, Mortensen PE, DOORS Study Group. On-pump versus off-pump coronary artery bypass surgery in elderly patients: results from the Danish on-pump versus off-pump randomization study. *Circulation*. 2012;125:2431–2439.

27. Hueb W, Lopes NH, Pereira AC, Hueb AC, Soares PR, Favarato D, Vieira RD, Lima EG, Garzillo CL, Paulitch F da S, César LAM, Gersh BJ, Ramires JAF. Five-Year Follow-Up of a Randomized Comparison Between Off-Pump and On-Pump Stable Multivessel Coronary Artery Bypass Grafting. The MASS III Trial. *Circulation*. 2010;122:S48–S52.

28. Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, Hill JA, Menicanti L, Sadowski Z, Desvigne-Nickens P, Rouleau J-L, Lee KL, STICH Hypothesis 2 Investigators. Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med*. 2009;360:1705–1717.

29. Karolak W, Hirsch G, Buth K, Légaré J-F. Medium-term outcomes of coronary artery bypass graft surgery on pump versus off pump: Results from a randomized controlled trial. *Am Heart J*. 2007;153:689–695.

30. Khan NE, De Souza A, Mister R, Flather M, Clague J, Davies S, Collins P, Wang D, Sigwart U, Pepper J. A Randomized Comparison of Off-Pump and On-Pump Multivessel Coronary-Artery Bypass Surgery. *N Engl J Med*. 2004;350:21–28.

31. Kobayashi J, Tashiro T, Ochi M, Yaku H, Watanabe G, Satoh T, Tagusari O, Nakajima H, Kitamura S, Japanese Off-Pump Coronary Revascularization Investigation (JOCRI) Study Group. Early outcome of a randomized comparison of off-pump and on-pump multiple arterial coronary revascularization. *Circulation*. 2005;112:I338-343.

32. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes J-C, Novick RJ, Vaijyanath P, Reddy SK, Tao L, Olavegogeascoechea PA, Airan B, Sulling T-A, Whitlock RP, Ou Y, Pogue J, Chrolavicius S, Yusuf S, CORONARY Investigators. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. *N Engl J Med*. 2013;368:1179–1188.

33. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes J-C, Novick RJ, Vaijyanath P, Reddy S, Tao L, Olavegogeascoechea PA, Airan B, Sulling T-A, Whitlock RP, Ou Y, Ng J, Chrolavicius S, Yusuf S, CORONARY Investigators. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med*. 2012;366:1489–1497.

34. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Straka Z, Piegas LS, Avezum A, Akar AR, Lanas Zanetti F, Jain AR, Noiseux N, Padmanabhan C, Bahamondes J-C, Novick RJ, Tao L, Olavegogeascoechea PA, Airan B, Sulling T-A, Whitlock RP, Ou Y, Gao P, Pettit S, Yusuf S, CORONARY Investigators. Five-Year Outcomes after Off-Pump or On-Pump Coronary-Artery Bypass Grafting. *N Engl J Med*. 2016;375:2359–2368.

35. Légaré J-F, Buth KJ, King S, Wood J, Sullivan JA, Friesen CH, Lee J, Stewart K, Hirsch GM. Coronary Bypass Surgery Performed off Pump Does Not Result in Lower In-Hospital Morbidity Than Coronary Artery Bypass Grafting Performed on Pump. *Circulation*. 2004;109:887–892.

36. Lemma MG, Coscioni E, Tritto FP, Centofanti P, Fondacone C, Salica A, Rossi A, De Santo T, Di Benedetto G, Piazza L, Rinaldi M, De Luca Tupputi Schinosa AL, De Paulis R, Contino M, Genoni M. On-pump versus off-pump coronary artery bypass surgery in high-risk patients: Operative results of a prospective randomized trial (on-off study). *J Thorac Cardiovasc Surg*. 2012;143:625–631.

37. Lingaas PS, Hol PK, Lundblad R, Rein KA, Mathisen L, Smith H-J, Andersen R, Thaulow E, Tønnesen TI, Svennevig JL, Hauge SN, Fredriksen PM, Andersen M, Fosse E. Clinical and Radiologic Outcome of Off-Pump Coronary Surgery at 12 Months Follow-Up: A Prospective Randomized Trial. *Ann Thorac Surg*. 2006;81:2089–2095.

38. Lingaas PS, Hol PK, Lundblad R, Rein KA, Tønnesen TI, Svennevig JL, Hauge SN, Vatne K, Fosse E. Clinical and Angiographic Outcome of Coronary Surgery with and without Cardiopulmonary Bypass: A Prospective Randomized Trial. *Heart Surg Forum*. 2004;7:37–41.

39. Michaux I, Filipovic M, Skarvan K, Bolliger D, Schumann R, Bernet F, Seeberger M. A randomized comparison of right ventricular function after on-pump versus off-pump coronary artery bypass graft surgery. *J Thorac Cardiovasc Surg*. 2011;141:361–367.

40. Michler RE, Smith PK, Parides MK, Ailawadi G, Thourani V, Moskowitz AJ, Acker MA, Hung JW, Chang HL, Perrault LP, Gillinov AM, Argenziano M, Bagiella E, Overbey JR, Moquete EG, Gupta LN, Miller MA, Taddei-Peters WC, Jeffries N, Weisel RD, Rose EA, Gammie JS, DeRose JJ, Puskas JD, Dagenais F, Burks SG, El-Hamamsy I, Milano CA, Atluri P, Voisine P, O'Gara PT, Gelijns AC, CTSN. Two-Year Outcomes of Surgical Treatment of Moderate Ischemic Mitral Regurgitation. *N Engl J Med*. 2016;374:1932–1941.

41. Moller CH, Perko MJ, Lund JT, Andersen LW, Kelbaek H, Madsen JK, Winkel P, Gluud C, Steinbruchel DA. No major differences in 30-day outcomes in high-risk patients randomized to off-pump versus on-pump coronary bypass surgery: the best bypass surgery trial. *Circulation*. 2010;121:498–504.

42. Møller CH, Perko MJ, Lund JT, Andersen LW, Kelbæk H, Madsen JK, Winkel P, Gluud C, Steinbrüchel DA. Three-year follow-up in a subset of high-risk patients randomly assigned to

off-pump versus on-pump coronary artery bypass surgery: the Best Bypass Surgery trial. *Heart Br Card Soc*. 2011;97:907–913.

43. Muneretto C, Bisleri G, Negri A, Manfredi J, Metra M, Nodari S, Dei Cas L. Off-pump coronary artery bypass surgery technique for total arterial myocardial revascularization: a prospective randomized study. *Ann Thorac Surg*. 2003;76:778–783.

44. Myers WO, Berg R, Ray JF, Douglas-Jones JW, Maki HS, Ulmer RH, Chaitman BR, Reinhart RA. All-artery multigraft coronary artery bypass grafting with only internal thoracic arteries possible and safe: a randomized trial. *Surgery*. 2000;128:650–659.

45. Nasso G, Coppola R, Bonifazi R, Piancone F, Bozzetti G, Speziale G. Arterial revascularization in primary coronary artery bypass grafting: Direct comparison of 4 strategies--results of the Stand-in-Y Mammary Study. *J Thorac Cardiovasc Surg*. 2009;137:1093–1100.

46. Nathoe HM, van Dijk D, Jansen EWL, Suyker WJL, Diephuis JC, van Boven W-J, de la Rivière AB, Borst C, Kalkman CJ, Grobbee DE, Buskens E, de Jaegere PPT, Octopus Study Group. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. *N Engl J Med*. 2003;348:394–402.

47. Pegg TJ, Selvanayagam JB, Karamitsos TD, Arnold RJ, Francis JM, Neubauer S, Taggart DP. Effects of off-pump versus on-pump coronary artery bypass grafting on early and late right ventricular function. *Circulation*. 2008;117:2202–2210.

48. Puskas JD, Williams WH, Mahoney EM, Huber PR, Block PC, Duke PG, Staples JR, Glas KE, Marshall JJ, Leimbach ME, McCall SA, Petersen RJ, Bailey DE, Weintraub WS, Guyton RA. 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;291:1841–1849.

49. Rogers CA, Pike K, Campbell H, Reeves BC, Angelini GD, Gray A, Altman DG, Miller H, Wells S, Taggart DP, CRISP investigators. Coronary artery bypass grafting in high-RISk patients randomised to off- or on-Pump surgery: a randomised controlled trial (the CRISP trial). *Health Technol Assess Winch Engl*. 2014;18:v–xx, 1–157.

50. Shahin GMM, van der Heijden GJMG, Bots ML, Cramer M-J, Jaarsma W, Gadellaa JCA, de la Rivière AB, van Swieten HA. The Carpentier-Edwards Classic and Physio mitral annuloplasty rings: a randomized trial. *Heart Surg Forum*. 2005;8:E389-394; discussion E394-395.

51. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, Lucke JC, Baltz JH, Novitzky D, Veterans Affairs Randomized On/Off Bypass (ROOBY) Study Group. On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med*. 2009;361:1827–1837.

52. Shroyer AL, Hattler B, Wagner TH, Collins JF, Baltz JH, Quin JA, Almassi GH, Kozora E, Bakaeen F, Cleveland JC, Bishawi M, Grover FL, Veterans Affairs ROOBY-FS Group. Five-Year Outcomes after On-Pump and Off-Pump Coronary-Artery Bypass. *N Engl J Med*. 2017;377:623–632.

53. Smith PK, Puskas JD, Ascheim DD, Voisine P, Gelijns AC, Moskowitz AJ, Hung JW, Parides MK, Ailawadi G, Perrault LP, Acker MA, Argenziano M, Thourani V, Gammie JS, Miller MA, Pagé P, Overbey JR, Bagiella E, Dagenais F, Blackstone EH, Kron IL, Goldstein DJ, Rose EA, Moquete EG, Jeffries N, Gardner TJ, O'Gara PT, Alexander JH, Michler RE,

Cardiothoracic Surgical Trials Network Investigators. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med*. 2014;371:2178–2188.

54. Sousa Uva M, Cavaco S, Oliveira AG, Matias F, Silva C, Mesquita A, Aguiar P, Bau J, Pedro A, Magalhães MP. Early graft patency after off-pump and on-pump coronary bypass surgery: a prospective randomized study. *Eur Heart J*. 2010;31:2492–2499.

55. Straka Z, Widimsky P, Jirasek K, Stros P, Votava J, Vanek T, Brucek P, Kolesar M, Spacek R. Off-pump versus on-pump coronary surgery: final results from a prospective randomized study Prague-4. *Ann Thorac Surg*. 2004;77:789–793.

56. Taggart DP, Altman DG, Gray AM, Lees B, Nugara F, Yu L-M, Campbell H, Flather M, ART Investigators. Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). *Eur Heart J*. 2010;31:2470–2481.

57. Taggart DP, Altman DG, Gray AM, Lees B, Gerry S, Benedetto U, Flather M, ART Investigators. Randomized Trial of Bilateral versus Single Internal-Thoracic-Artery Grafts. *N Engl J Med*. 2016;375:2540–2549.

58. Taggart DP, Benedetto U, Gerry S, Altman DG, Gray AM, Lees B, Gaudino M, Zamvar V, Bochenek A, Buxton B, Choong C, Clark S, Deja M, Desai J, Hasan R, Jasinski M, O'Keefe P, Moraes F, Pepper J, Seevanayagam S, Sudarshan C, Trivedi U, Wos S, Puskas J, Flather M, Arterial Revascularization Trial Investigators. Bilateral versus Single Internal-Thoracic-Artery Grafts at 10 Years. *N Engl J Med*. 2019;380:437–446.

59. Yu L, Gu T, Shi E, Wang C, Fang Q, Yu Y, Zhao X, Qian C. Off-pump versus on-pump coronary artery bypass surgery in patients with triple-vessel disease and enlarged ventricles. *Ann Saudi Med*. 2014;34:222–228.

60. Zenati MA, Bhatt DL, Bakaeen FG, Stock EM, Biswas K, Gaziano JM, Kelly RF, Tseng EE, Bitondo J, Quin JA, Almassi GH, Haime M, Hattler B, DeMatt E, Scrymgeour A, Huang GD, REGROUP Trial Investigators. Randomized Trial of Endoscopic or Open Vein-Graft Harvesting for Coronary-Artery Bypass. *N Engl J Med*. 2019;380:132–141.