

Long-Term Outcomes of On- Versus Off-Pump Coronary Artery Bypass Grafting



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ABSTRACT

BACKGROUND When comparing effects of on- versus off-pump coronary artery bypass grafting (CABG), it is important to assess the long-term clinical outcomes. However, most research conducted thus far has concentrated on short-term outcomes and ignored the long-term clinical outcomes, especially the 5-year outcomes of the largest randomized controlled trials.

OBJECTIVES The aim of this systematic review and meta-analysis was to investigate the long-term clinical outcomes of on- versus off-pump CABG.

METHODS To identify potential studies systematic searches were carried out using various databases. The search strategy included the key concepts of *cardiopulmonary bypass AND off-pump AND long term OR 5-year outcomes*. This was followed by a meta-analysis investigating mortality, incidence of myocardial infarction, incidence of angina, need for revascularization, and incidence of stroke.

RESULTS Six studies totaling 8,145 participants were analyzed. In the on-pump group mortality was 12.3%, compared with 13.9% in the off-pump group. The odds ratio (OR) for this comparison was 1.16 (95% confidence interval [CI]: 1.02 to 1.32; $p = 0.03$; 13.9% vs. 12.3%). In contrast, there were no differences in the incidence of myocardial infarction (OR: 1.06; 95% CI: 0.91 to 1.25; $p = 0.45$; 8.4% vs. 7.9%), incidence of angina (OR: 1.09; 95% CI: 0.75 to 1.57; $p = 0.65$; 2.3% vs. 2.1%), need for revascularization (OR: 1.15; 95% CI: 0.95 to 1.40; $p = 0.16$; 5.9% vs. 5.1%), and the incidence of stroke (OR: 0.78; 95% CI: 0.56 to 1.10; $p = 0.16$; 2.2% vs. 2.8%).

CONCLUSIONS Statistically, on-pump CABG appeared to offer superior long-term survival, although the clinical significance of this may be more uncertain. (J Am Coll Cardiol 2018;71:983-91) © 2018 by the American College of Cardiology Foundation.

First introduced in the mid-1960s, coronary artery bypass grafting (CABG) is the gold standard treatment for patients with extensive coronary artery disease (1). The first successful open-heart operation using cardiopulmonary bypass was carried out in 1952 (2). The development and success of this approach has undoubtedly contributed to the decline in deaths due to coronary artery disease that has occurred in developed countries during the last 5 decades (1). However, coronary revascularization on cardiopulmonary bypass with its attendant aortic manipulation has been implicated in various complications including

increased risk of stroke (3,4) and stimulation of a systemic inflammatory response (5). This led in the mid-1980s to renewed interest in performing CABG on the beating heart (6) helped by the development of various stabilizing devices (7), despite the increased difficulty of this approach (5). Since that time there has been ongoing debate as to which technique is superior including several meta-analyses that have not fully answered the question (3,4,8,9). A good illustration of the dichotomy is the fact that 95% of CABGs in India are performed off pump (5), whereas the figure in the United Kingdom is approximately 20% (10).



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Manuscript received November 6, 2017; accepted December 19, 2017.

**ABBREVIATIONS
AND ACRONYMS**

- CABG** = coronary artery bypass grafting
- CI** = confidence interval
- MI** = myocardial infarction
- OR** = odds ratio
- RCT** = randomized controlled trial

The most important factor governing the choice of whether to choose on or off pump is the long-term outcomes. Until now, these have been difficult to assess due to the sparsity of long-term reporting from randomized controlled trials (RCTs). Some resolution to this problem has recently occurred with the publication of the 5-year outcomes of 2 of the largest RCTs to date, namely the ROOBY (Randomized On/Off Bypass) (11) and CORONARY (CABG Off or On Pump Revascularisation Study) (12) trials. Therefore, the aim of this systematic review was to synthesize the results from all studies reporting the long-term (>4 years) clinical outcome of RCTs that investigated on- versus off-pump CABG. This is the first meta-analysis to only consider long-term results from RCTs and to include the results from the ROOBY and CORONARY trials.

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METHODS

SEARCH STRATEGY. To identify potential studies, systematic searches were carried out using the

following databases: Embase, PubMed, Web of Science, and the Cochrane Central Registry of Controlled Trials. The search was supplemented by scanning the reference lists of eligible studies. The search strategy included the key concepts of *cardiopulmonary bypass AND coronary artery bypass grafting AND off-pump AND long term OR 5-year outcomes*. Two reviewers assessed all identified papers independently. A third reviewer was consulted to resolve disputes. Searches of published papers were conducted up until September 1, 2017.

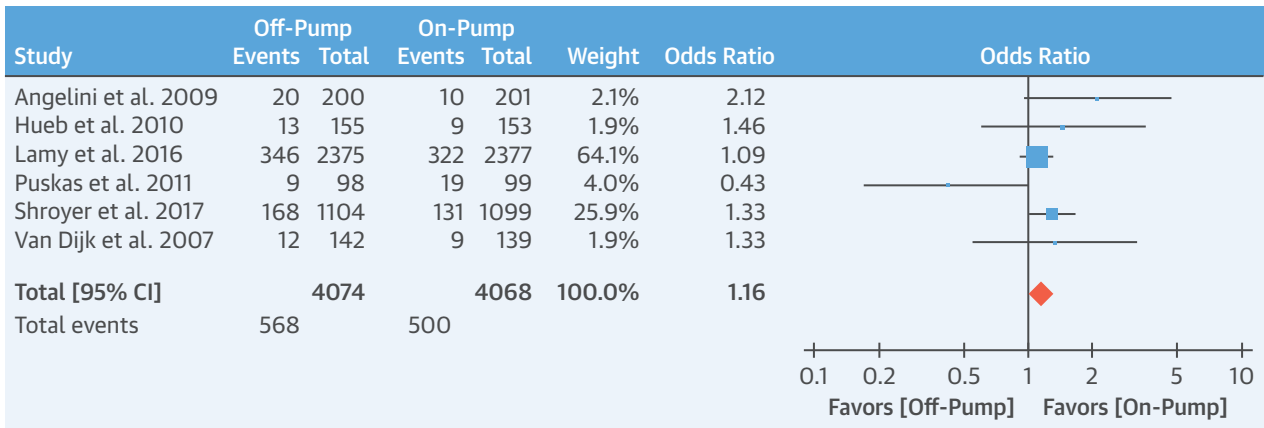
TYPES OF STUDIES TO BE INCLUDED. This meta-analysis only included studies reporting long-term (>4 years) outcomes from RCTs of off pump versus on pump in patients undergoing CABG. There were no language restrictions. Animal studies, review papers, and nonrandomized controlled trials were excluded. Studies that did not have any of the desired outcome measures or participants who were treated by other modalities such as percutaneous coronary intervention were excluded. Incomplete data were excluded. Studies that included interventions other than off-pump versus on-pump CABG were excluded.

TABLE 1 Characteristics of Included Trials

| First Author (Ref. #), Country | OnCPB vs. OffCPB | | Yrs of Follow-Up | Men (%) OnCPB vs. OffCPB | All Outcome Measures |
|---------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------|---------------------|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| | N | Age (yrs), Mean ± SD | | | |
| Angelini et al. (10), England | BHACAS 1: 100 vs. 100 BHACAS 2: 101 vs. 100 | BHACAS 1: 61.7 ± 8.6 vs. 62.2 ± 9.6 BHACAS 2: 61.2 ± 9.2 vs. 63.8 ± 8.5 | >4 >4 | BHACAS 1: 79 vs. 82 BHACAS 2: 85 vs. 82 | Angina Graft patency MI Mortality Quality of life Revascularization |
| Van Dijk et al. (15), the Netherlands | 139 vs. 142 | 60.8 ± 8.8 vs. 61.7 ± 9.2 | 5 | 70.5 vs. 66.2 | Cognitive outcomes MI Mortality Quality of life Revascularization Stroke |
| Hueb et al. (16), Brazil | 155 vs. 156 | 59 vs. 61 | 5 | 80 vs. 78 | Angina MI Mortality Positive treadmill test Revascularization Stroke |
| Lamy et al. (12), United States | 2,377 vs. 2,375 | 67.5 ± 6.9 vs. 67.6 ± 6.7 | 5 | 81.7 vs. 80 | Angina Costs per patient MI Mortality New renal failure Quality of life Revascularization Stroke |
| Puskas et al. (17), United States | 99 vs. 98 | 62.2 ± 11.1 vs. 62.5 ± 9.5 | 5 | 77 vs. 78 | Graft patency Mortality |
| Shroyer et al. (11), United States | 1,099 vs. 1,104 | 64 ± 11 vs. 68 ± 9 | 5 | 62.5 ± 8.5 vs. 63.0 ± 8.0 | MI Mortality Revascularization |

BHACAS = beating heart against cardioplegic arrest study; MI = myocardial infarction; OffCPB = off-pump cardiopulmonary bypass; OnCPB = on-pump cardiopulmonary bypass.

CENTRAL ILLUSTRATION Long-Term Outcomes After On- Versus Off-Pump CABG: Forest Plot of Mortality Incidence



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This shows that the odds of mortality occurrence were significantly greater in the off-pump group compared with the on-pump group. Summary statistics for each study are shown in the table on the left with each study's odds ratio (square).

PARTICIPANTS AND POPULATION. Only studies reporting the long-term outcomes (>4 years) of RCTs of both male and female adult (≥18 years of age) patients with coronary artery disease who were undergoing CABG either off or on pump were included.

INTERVENTION(S), EXPOSURE(S). This meta-analysis considered all studies reporting the long-term (>4 years) outcomes from RCTs where patients with stable angina or acute coronary syndrome being treated with CABG were exposed to either on pump or off pump. More specifically, all long-term (>4 years) studies directly derived from RCTs where the intervention of carrying out CABG without the use of cardiopulmonary bypass.

COMPARATOR(S) AND CONTROL GROUP. The studies in this analysis compared the long-term outcomes of off-pump CABG with a usual-care control group receiving on-pump CABG.

SEARCH RESULTS. Our initial search found 204 articles. The majority of these studies were excluded because they were not RCTs. Four studies were excluded because they were retrospective analyses, 4 studies were excluded because they only reported short-term outcomes, 1 study was excluded because it had no comparator group, and 1 study was excluded because it duplicated data (Online Figure 1). Six studies were included in our analysis.

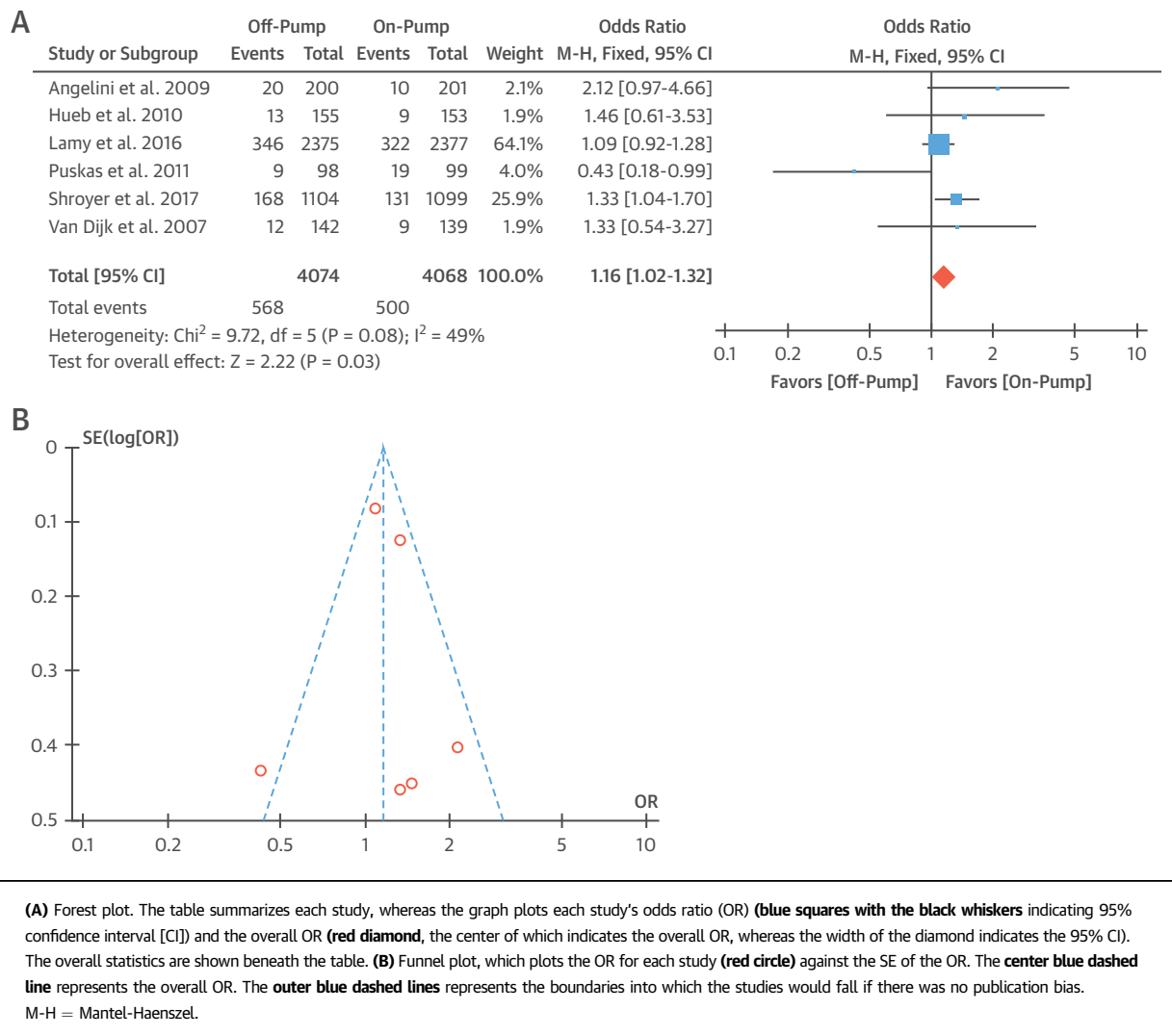
OUTCOME(S). The primary outcomes analyzed were: mortality, incidence of myocardial infarction (MI), angina, requirement for revascularization, and incidence of stroke.

RISK OF BIAS (QUALITY) ASSESSMENT. Risk of bias was assessed using a modification of the Jadad scale (13).

STRATEGY FOR DATA SYNTHESIS. Odds ratios (ORs) were calculated for dichotomous data. An OR is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared with the odds of the outcome occurring in the absence of that exposure. All analyses were conducted using Revman 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). A fixed-effects inverse variance model was used throughout. Heterogeneity was quantified using the Cochrane Q test (14). We used a 5% level of significance and 95% confidence intervals; figures were produced using Revman 5.3.

RESULTS

The 6 studies (10,12,13,15-17) included in the analyses had an aggregate of 8,145 participants, 4,069 of whom had on-pump CABG and 4,076 of whom had off-pump CABG. Table 1 summarizes the characteristics of the

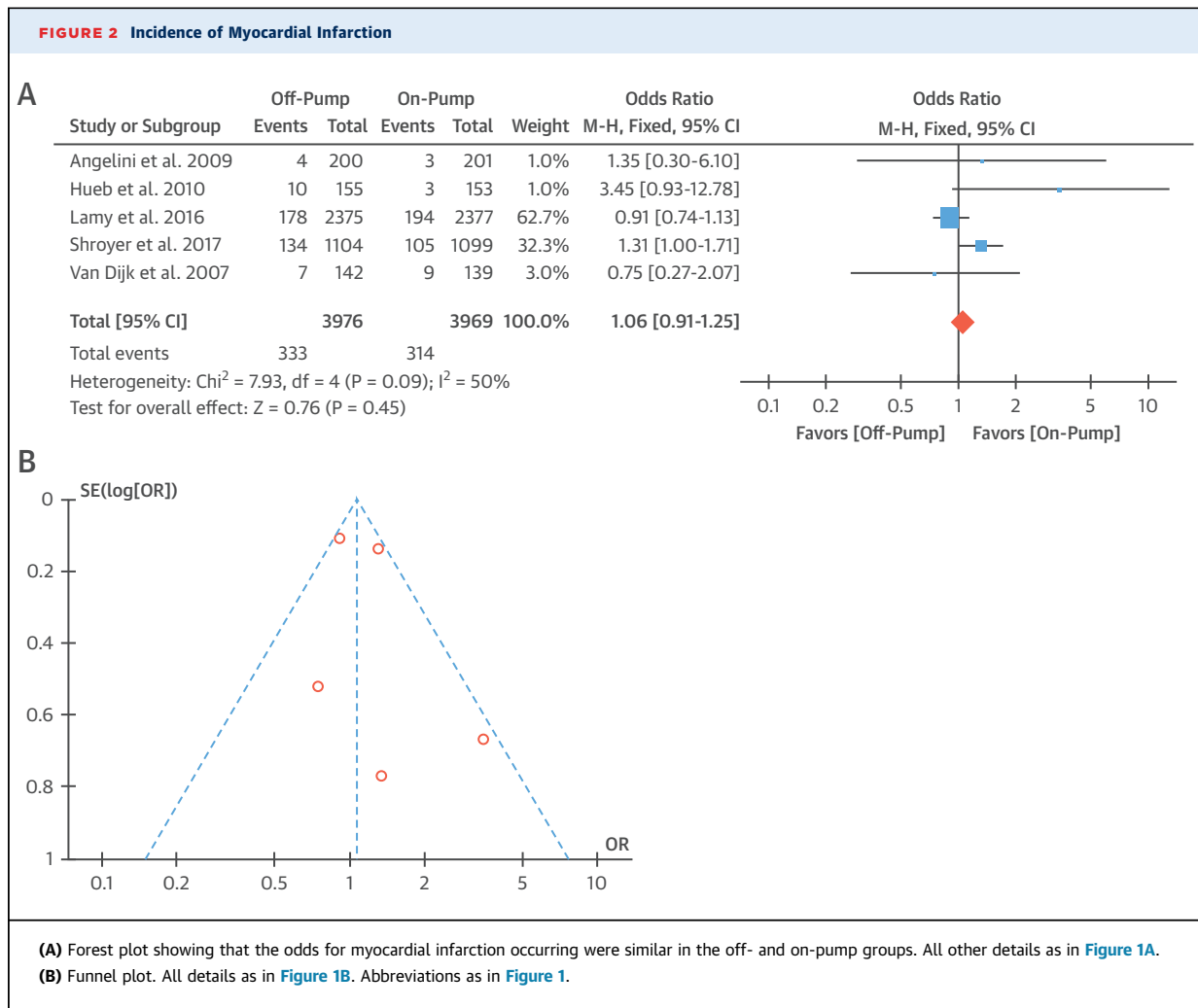
FIGURE 1 Mortality Incidence

included studies. [Online Table 1](#) lists the excluded RCTs and reasons for exclusion. Angelini et al. (10) reported the clinical outcomes at >4 years, whereas the remainder of studies reported outcomes at 5 years (12,13,15-17).

MORTALITY. All of the studies reported the incidence of mortality. In total, 568 of 4,074 (13.9%) patients of the off-pump patients had died at follow-up compared with only 500 of 4,068 (12.3%) of the on-pump patients. The OR for the comparison was 1.16 (95% confidence interval [CI]: 1.02 to 1.32; $I^2 = 49\%$; $Z = 2.22$; $p = 0.03$) (Figure 1A). The odds of dying were significantly greater in the off-pump group compared with the odds of dying in the on-pump group. The funnel plot was symmetrical (Figure 1B).

MI INCIDENCE. Five studies reported the incidence of MI. In total, 333 of 3,976 (8.4%) patients had an MI in the off-pump group compared with 314 of 3,969 (7.9%) patients in the on-pump group. The OR was 1.06 (95% CI: 0.91 to 1.25; $I^2 = 50\%$; $Z = 0.76$; $p = 0.45$) (Figure 2A). There was no significant difference in the odds of having an MI between the 2 groups. The funnel plot was symmetrical (Figure 2B).

ANGINA INCIDENCE. Three studies reported the incidence of angina. In total, 62 of 2,731 (2.3%) off-pump patients were experiencing angina compared with 57 of 2,730 (2.1%) on-pump patients. The OR was 1.09 (95% CI: 0.75 to 1.57; $I^2 = 54\%$; $Z = 0.45$; $p = 0.65$) (Figure 3A). The likelihood that patients were experiencing angina was similar in each group. The funnel plot was symmetrical (Figure 3B).



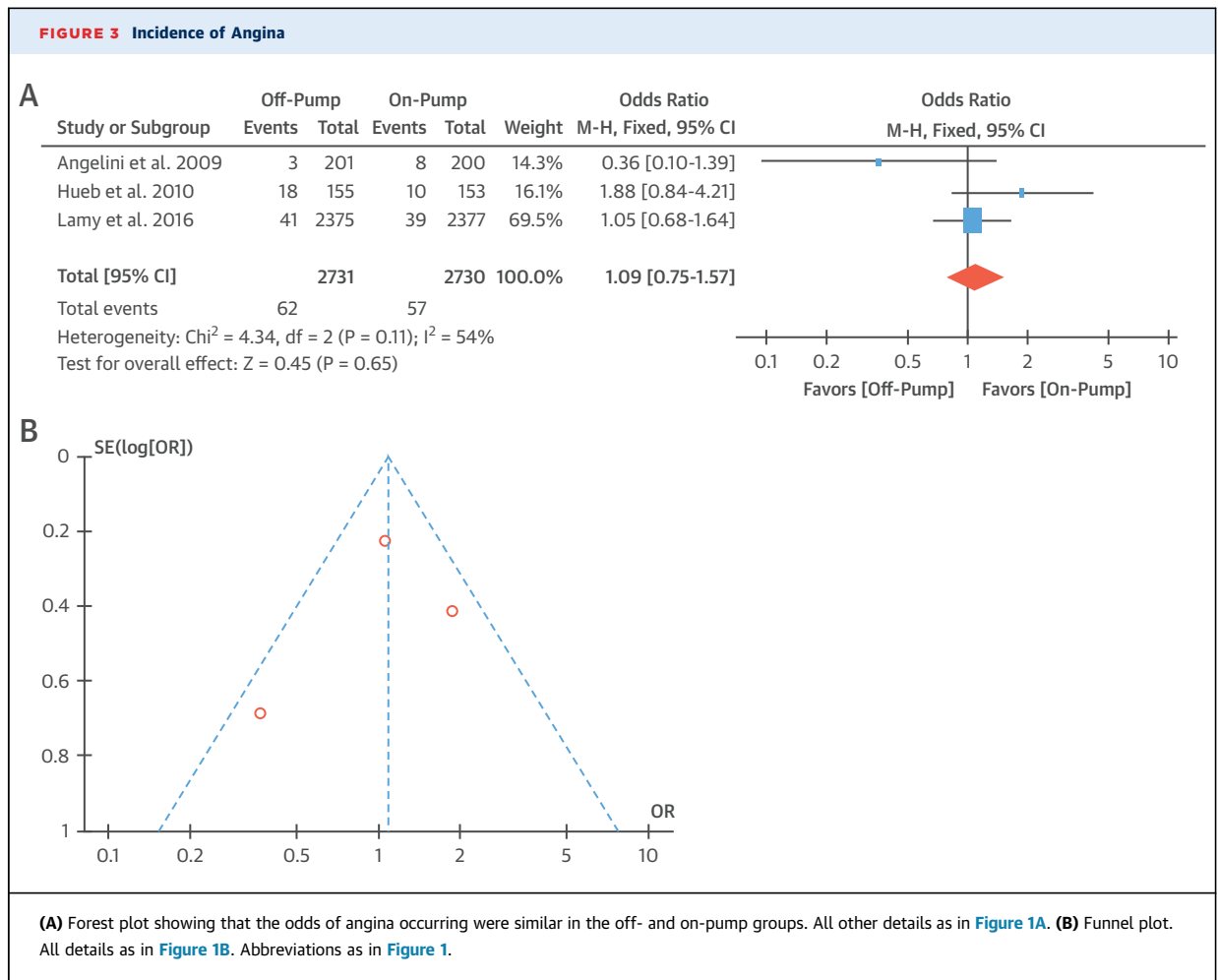
REQUIREMENT FOR REVASCUARIZATION. Five studies reported the need for revascularization. In total 233 of 3,976 (5.9%) off-pump patients required revascularization compared with 204 of 3,969 (5.1%) on-pump patients. The OR was 1.15 (95% CI: 0.95 to 1.40; $I^2 = 0\%$; $Z = 1.41$; $p = 0.16$) ([Figure 4A](#)). There was no significant difference in the odds of requiring revascularization between each group. The funnel plot was symmetrical ([Figure 4B](#)).

STROKE INCIDENCE. Three studies reported the incidence of stroke. In total 60 of 2,672 (2.2%) off-pump patients had a stroke compared with 76 of 2,669 (2.8%) on-pump group. The OR was 0.78 (95% CI: 0.56 to 1.10; $I^2 = 0\%$; $Z = 1.39$; $p = 0.16$) ([Figure 5A](#)). There was no significant difference in the odds of a stroke occurring in the off-pump group as in the on-pump group. The funnel plot was symmetrical ([Figure 5B](#)).

STUDY QUALITY. The modified Jadad scale of study quality revealed a median score of 3.5 ([Online Table 2](#)). The quality of the studies varied from a low score of 2 to a high score of 4. More than 50% of the studies described the method of randomization; however, no studies described the method of blinding for which it should be noted that it is impossible to blind the surgeon as to whether (s)he is performing off- or on-pump CABG.

DISCUSSION

This is the first meta-analysis to consider the long-term (>4 years of follow-up) clinical effects of on-versus off-pump CABG using only RCTs and including the 5-year outcomes of 2 of the largest RCTs to date ([11,12](#)). The results presented here suggest that there is a significantly lower mortality incidence in the

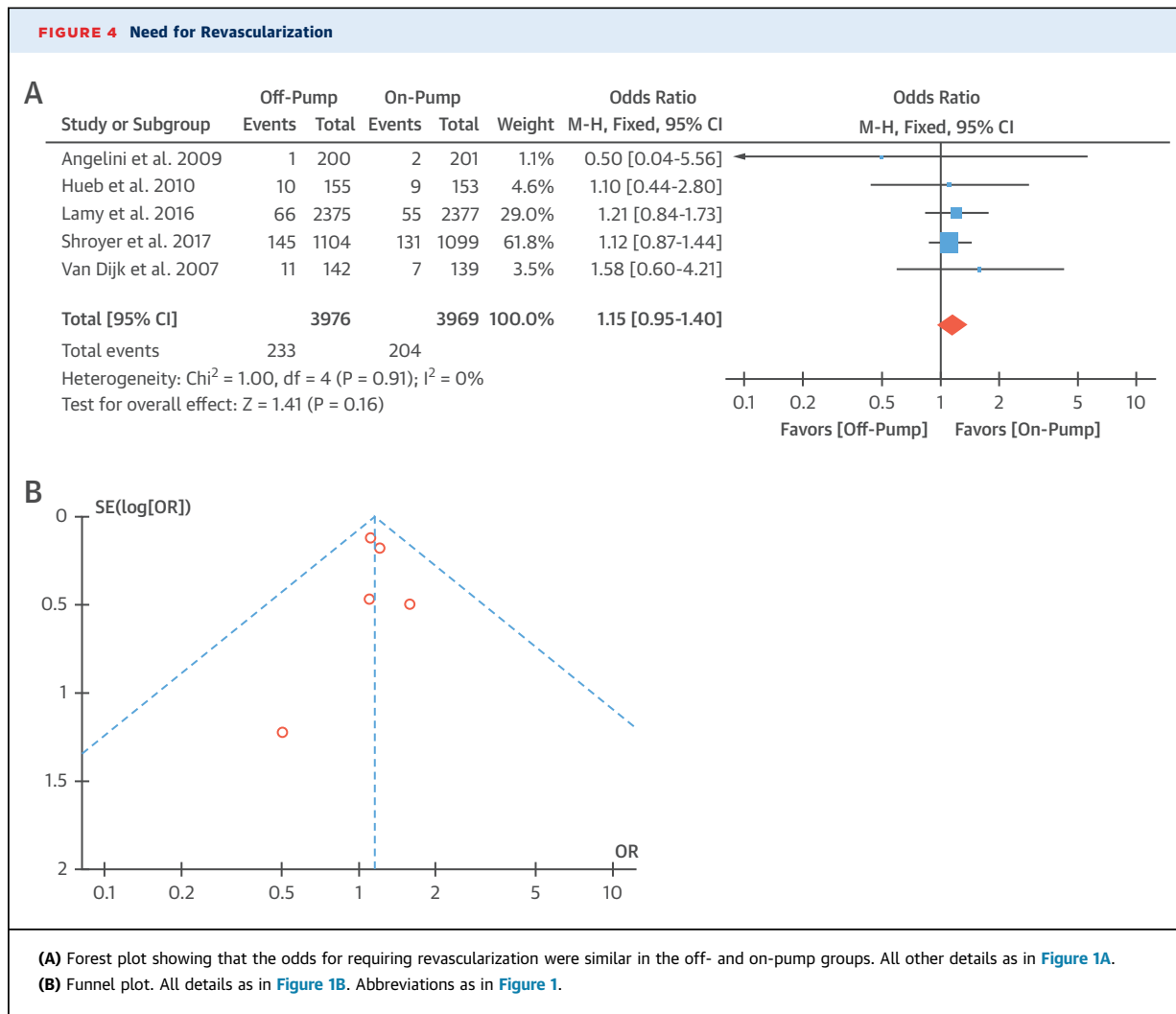


on-pump group, whereas the incidence of MI, angina, revascularization, and stroke were similar in both groups ([Central Illustration](#)).

Meta-analyses pool results from all included trials without focusing on one trial over another. With the exception of Puskas et al. ([17](#)), all of the RCTs included had higher rates of mortality in the off-pump group; however, only in the case of the ROOBY trial did this reach significance. It has been suggested that this might be due to differences in the surgeons' experience. The CORONARY trial ([12](#)) demanded that all of the surgeons had at least 2 years' experience of performing off-pump CABG, whereas the ROOBY trial only required surgeons to have experience of 120 cases (median 50) ([11](#)).

This meta-analysis concentrated on prospective RCTs; however, there have been other large retrospective studies that have investigated long-term survival. On the whole, these studies have shown no difference in mortality between off-pump and

on-pump CABG ([18](#)). In the 2 exceptions, long-term survival rates were significantly better in the on-pump group. This bears some similarities to the current meta-analysis in which individual studies showed no differences in survival but the overall mortality was statistically in favor of the on-pump group, although whether the absolute difference is of clinical significance may be more uncertain. Two of the factors that could contribute to long-term outcomes are graft patency and completeness of revascularization. Related to this are concerns that performing CABG off-pump means that distal anastomoses are performed on the beating heart ([9](#)). These disquiets appeared to be supported by the short-term outcomes of the CORONARY and ROOBY trials, which showed lower graft patency and higher rates of revascularization in the off-pump group ([19,20](#)). It is therefore noteworthy that at 5 years MI, angina, and revascularization were not significantly different in the 2 groups. In accordance with this



Angelini et al. (10) and Puskas et al. (17) specifically studied graft patency at >4 years and found there to be no difference.

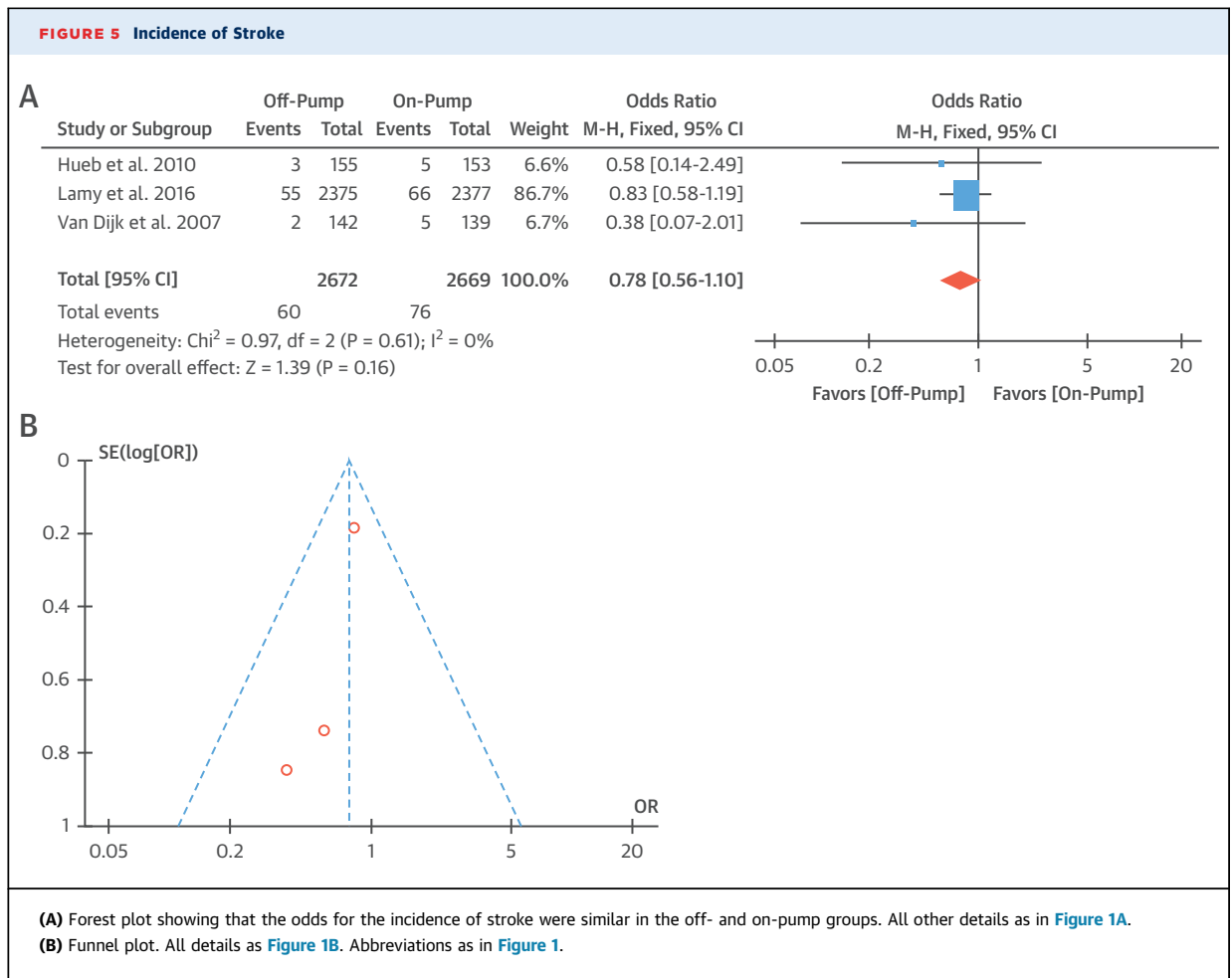
The incidence of stroke following CABG is approximately 2.0% to 3.7% (21,22), where the 5-year outcomes of the SYNTAX (The SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery) trial showed the incidence of stroke to be insignificantly different between CABG and PCI (22). This meta-analysis concentrated on long-term clinical outcomes, which showed there to be no difference in the incidence of stroke between the 2 groups. A recent network meta-analysis showed that avoiding aortic manipulation in the off-pump group significantly reduced the incidence of stroke at 30 days (23). A lower incidence of stroke in the off-pump group at 30 days was also found in 2 of the

recent meta-analyses (3,4), although the third found no difference (8).

STUDY LIMITATIONS. Myocardial protection during on-pump CABG varied between studies. For instance, although Angelini et al. (24) and Puskas et al (7) used hyperkalemic warm blood cardioplegia, Hueb et al. (16) used cold crystalloid cardioplegia. The majority of the studies used the Octopus stabilizer (Medtronic, Minneapolis, Minnesota).

The median study quality score was moderate with studies scoring between 2 and 4 on a scale of 6. There was also some evidence of heterogeneity in a number of the analyses. It should be noted though that the funnel plots were all symmetrical.

It is impossible to blind the surgeon as to which type of surgery they are to perform. However, not all studies reported the method of randomization and



described withdrawals and dropouts. This would be something that future studies may like to take into account.

CONCLUSIONS

After more than 4 years of follow-up, off-pump CABG was associated with higher all-cause mortality compared with on-pump CABG. All other comparisons including revascularization, MI, and angina were insignificantly different.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: On-pump CABG surgery is associated with long-term survival that is statistically superior and clinically noninferior to that with off-pump surgery.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to compare specific outcomes of on- versus off-pump CABG in well-defined patient populations.

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KEY WORDS CABG, long-term clinical outcomes, off pump, on pump

APPENDIX For a supplemental figure and tables, please see the online version of this paper.