



Systematic comparison of the effectiveness of radial artery and saphenous vein or right internal thoracic artery coronary bypass grafts in non-left anterior descending coronary arteries

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Abstract: Coronary artery bypass grafting surgery is increasingly being carried out on patients with multi-vessel coronary artery disease, but the best grafting candidate for non-left anterior descending coronary arteries is unclear. This research sought to systematically compare the efficacies and safeties of coronary bypass with radial artery and other available grafts. A systematic literature retrieval was performed for all clinical trials comparing the outcomes of coronary artery bypass surgery with radial artery and other grafts in PubMed, EMBASE, and the Cochrane Library. Seven eligible clinical studies, comparing radial artery and great saphenous vein grafts, were found between 1966 and 2010: one prospective non-randomized and six prospective randomized trials. The pooling analysis obtained a relative risk of 0.507 ($P < 0.05$) of graft occlusion in radial arteries compared with great saphenous veins. There was a significantly lower infection rate in arms (i.e., harvest sites for radial arteries) relative to legs (harvest sites for veins), with a pooled relative risk of 0.140 ($P < 0.05$). From the reports on mortality after follow-up ranging from one year to six years, there was no significant difference in mortality between the two graft types ($P = 0.927$). In addition, four cohort controlled trials for radial and right internal thoracic artery grafts were included. The radial graft was associated with less cardiac related events relative to the right internal thoracic artery graft ($P = 0.014$), but with comparable mortality and comparable rates of repeat percutaneous transluminal coronary angioplasty. Subjects with radial arteries seemed to have a lower occlusion rate and a lower graft harvest site infection rate than those with great saphenous veins. Moreover there were fewer cardiac related events with radial arteries relative to the right internal thoracic artery grafts. More studies are needed to confirm these findings concerning the favorable outcomes of coronary artery bypass grafting with radial arteries on long-term patency and mortality.

Key words: Coronary artery bypass grafting (CABG), Arterial grafts, Meta-analysis

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1 Introduction

Therapeutic options available for multi-vessel coronary artery diseases include medical therapy only, percutaneous transluminal coronary intervention (PCI) with stents, and coronary artery bypass grafting (CABG). In terms of efficacy and safety, the former two procedures are limited to the early, single, and

discrete lesions. CABG surgery, no doubt, plays a vital role in more extensive, diffuse, and multiple vessel disease cases. Hence, the left internal thoracic artery only, the gold standard graft to the left anterior descending coronary artery (LAD), cannot meet the actual clinical need for more high quality conduits. The use of arterial conduits has been increasing in light of evidence of more encouraging patency and clinical outcomes, although the great saphenous vein remains the most common conduit for revascularization. In the past 15 years, a dramatic increase in the use of arterial

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grafts has been witnessed, following the revival of the use of the radial artery conduit published by Lytle *et al.* (1999), a variety of observational clinical analyses, and randomized control studies. On the contrary, at five-year follow-up, one prospective randomized trial indicated comparable patency with no difference between the two grafts: radial artery and saphenous vein (Buxton *et al.*, 2003). Meanwhile, the right internal thoracic artery also appears to be an alternative as the second arterial graft source, showing improved survival in two internal thoracic artery graft studies (Taggart *et al.*, 2001). Given that coronary surgery with arterial grafts is becoming more popular, an evaluation of CABG with radial artery conduit on graft patency, site complication, and the morality compared with other conduits is imperative.

2 Materials and methods

2.1 Search strategy

A systematic literature retrieval was performed in PubMed (1966 to 2010), EMBASE (1974 to 2010), and the Cochrane Library (2010). We employed the key words “myocardial revascularization, coronary artery bypass, CABG, coronary surgery, radial artery, and clinical trial”. In order to broaden the range of the retrieval, all controlled trials of CABG surgery with radial and other grafts were viewed individually. Moreover, the abstracts from major cardiology and cardiac surgery meetings available between 2003 and 2010 were manually retrieved. References in these papers were also reviewed irrespective of language, and we even attempted to correspond with authors of relevant studies.

Two reviewers independently abstracted information from each study for study title, authors, publication year, institution, population profiles, cardiovascular risk factors, number of native relevant coronary arteries, study design, follow-up, inclusion and exclusion criteria, and main outcomes of graft failure (mortality and conduit harvest site infection). If studies showing results at several different points in follow-up were published by the same investigators, population profiles in the first report were included in our study, along with information on outcomes at subsequent follow-up

periods abstracted from the study reported later. When there were several reports with the identical results followed up at similar time periods by the same group, those with better quality and more information were chosen for inclusion. Discordances were resolved by re-review or consensus review.

2.2 Study selection

All controlled trials evaluating CABG with radial arteries and other control grafts anastomosed to non-left anterior descending coronary branches were enrolled. Studies were included regardless of population demography, publication year, conference proceedings, or language. We excluded studies if the composite artery conduits were not defined clearly, or if the publication did not provide the outcomes of interest, or if the pooling results could not be analyzed from the presenting data. Absence of a control group, of course, was within our exclusion criteria.

2.3 Quality assessment

We undertook predetermined criteria to evaluate the qualities of included randomized trials (Jadad *et al.*, 1996). The assessment was based on the randomization methods, the use of intention-to-treat analysis, the report of dropout rates, allocation concealment, and the extent to which valid results were depicted.

2.4 Statistical analysis

This systematic assessment was performed according to a meta-analysis guideline recommended by Cochrane Collaboration Group (Clarke and Oxman, 2001). We employed relative risk (RR) as the summary statistic for categorical data, demonstrating the adverse ratio in the study group (radial artery conduit) relative to control group (great saphenous vein conduit or others). An RR with value <1 was in favor of the study group, and the RR was taken as statistically significant when the P value was 0.05 and the 95% confidence interval (CI) excluded 1. A fixed effects model was chosen on the presumption that variation in the individual trial results occurred in a true mean. Conversely, the random model was adopted. The heterogeneity for summary effects was calculated through the statistics of χ^2 and I^2 , and an I^2 value of more than 50% was regarded as reflecting heterogeneity. In the analysis of sensitivity, repeating the analysis with another effect model or omitting data in

low quality trials was performed. All statistical analyses were carried out with Stata 10 (StataCorp, College Station, Tex).

3 Results

3.1 Trial flow and characteristics

Our searches for clinical trials, comparing the efficacy of CABG surgery with radial and other conduits, yielded 121 potentially relevant articles. Of these, 90 articles were excluded for only dealing with PCI as a myocardial revascularization procedure, and 10 were excluded owing to not having included conventional surgery as a control arm or no concrete arterial conduits studied besides the radial artery. Then a total of 21 articles reporting on clinical trials met our inclusion criteria preliminarily, of which seven articles were ruled out for reporting the same trials with different perspectives, and one was excluded because of insufficient information on extraction. In the end, the data from seven clinical studies (Hata *et al.*, 2002; Muneretto *et al.*, 2004;

Zacharias *et al.*, 2004; Gaudino *et al.*, 2005; Collins *et al.*, 2008; Hayward *et al.*, 2008; Singh *et al.*, 2008) with comparison for radial and great saphenous vein grafts, were eligible in this study. In addition, five publications (Lemma *et al.*, 2001; Caputo *et al.*, 2003; Hayward *et al.*, 2007; 2010; Miana *et al.*, 2007) in four trials comparing radial and right internal thoracic artery grafts were retrieved for analysis. Finally, only one comparative study (Santos *et al.*, 2002) of radial artery and right gastroepiploic artery for CABG was found, which had no other trial for pooling analysis, so it was excluded.

These studies totaled 3889 subjects. The age of study enrollment averaged 62.5 years, ranging from 58 to 77 years. In total, 21% of subjects had diabetes mellitus, and the proportion of female subjects ranged from 4% to 44%. The study designs were prospective randomized in six studies, and one prospective matched design was found by comparing radial and great saphenous vein grafts. The four studies for radial and right internal thoracic artery grafts were: two retrospective, one prospective matched, and one prospective randomized designs (Table 1).

Table 1 Designs and patient characteristics for studies included in meta-analysis

No.	Study	Country	Design	Inclusion criteria	Follow up (month)	Mean age (year)*	Number of female*	Number of diabetes*
1	Singh <i>et al.</i> , 2008	Canada	Prospective random	3-vessel, non-LAD	12.0	61/61	75/75	148/148
2	Collins <i>et al.</i> , 2008	UK	Prospective random	Multi-vessel, circumflex	60.0	58/59	3/2	15/10
3	Hayward <i>et al.</i> , 2008	Australia	Prospective random	>1 vessel, non-LAD	74.0	72.5/73.1	22/21	50/52
4	Gaudino <i>et al.</i> , 2005	Italy	Prospective random	>2 vessels, OM, in stent stenosis	52.0			
5	Muneretto <i>et al.</i> , 2004	USA	Prospective random	3-vessel, non-LAD, age >70 years	16.0	77.3/76.8	35/37	39/36
6	Hata <i>et al.</i> , 2002	Australia	Prospective random	>1 vessel, non-LAD	3.0	66.0/65.9	20/18	17/32
7	Zacharias <i>et al.</i> , 2004	USA	Prospective match	3-vessel, non-LAD	60.0	63/63	260/258	343/350
8	Miana <i>et al.</i> , 2007	Brazil	Retrospective	>1 vessel, non-LAD	1.0	56/57	9/4	8/3
9	Hayward <i>et al.</i> , 2010	Australia	Prospective random	>1 vessel, non-LAD, age <70 years	66.0	59.2/59.5	23/18	22/20
10	Caputo <i>et al.</i> , 2003	UK	Prospective match	>1 vessel, non-LAD	18.0	57.7/55.5	51/29	59/21
11	Lemma <i>et al.</i> , 2001	Italy	Retrospective	>1 vessel, non-LAD, age <70 years	8.1	60/57	19/8	30/7

Non-LAD: non-left anterior descending artery; OM: obtuse marginal coronary; * Radial artery vs. other grafts

3.2 Quality of the inclusion

The qualities of included studies for radial and great saphenous vein grafts were regarded as high, and four studies (Gaudino *et al.*, 2005; Collins *et al.*, 2008; Hayward *et al.*, 2008; Singh *et al.*, 2008) obtained a grade of good, as the authors clearly disclosed the method of randomization, dropout rate and reason, and the intention-to-treat analysis. As well, allocation concealment was performed. Owing to a lack of declaration that allocation concealment or intention-to-treat analysis was used, two trials (Hata *et al.*, 2002; Muneretto *et al.*, 2004) obtained a moderate grade. We assigned poor quality to one trial (Zacharias *et al.*, 2004) because of the matched pattern of its design type not to mention blinding, allocation concealment, or intention-to-treat analysis (Table 2). Relatively speaking, the qualities of trials for radial and right internal thoracic artery grafts were poor owing to retrospective (Lemma *et al.*, 2001; Miana *et al.*, 2007) and matched designs (Caputo *et al.*, 2003), except for one prospective randomized study (Hayward *et al.*, 2007; 2010).

Table 2 Quality assessments of the randomized clinical studies included

Study No.*	Score				Total
	Allocation concealment	Blinding	Random generator	Lost to follow-up	
1	2	1	1	1	5
2	2	0	2	0	4
3	2	0	2	1	5
4	1	1	2	1	5
5	1	0	0	0	1
6	1	0	0	0	1

* As shown in Table 1

3.3 Outcomes of interest

3.3.1 Comparison between radial and great saphenous vein grafts

1. Graft occlusion

Six studies presented data on graft occlusion over the maximum follow-up periods, ranging from one to six years. Of these, five were randomized studies and four contained groups that were followed up for at least 52 months. Hayward *et al.* (2007) showed that the graft failure rates at five years were similar for radial arteries and great saphenous veins. However,

the remaining trials all suggested the superiority of radial arteries in patency, compared to vein conduits. The pooling analysis calculated an RR of 0.507 (95% CI 0.411–0.626, $P < 0.05$) in graft occlusion with radial arteries compared to great saphenous veins, with no statistical heterogeneity ($\chi^2 = 6.31$, $P = 0.277$). The attributable heterogeneity (I^2) was 20.8% (Fig. 1). Meanwhile, there existed no bias ($P = 0.707$) (Fig. 2).

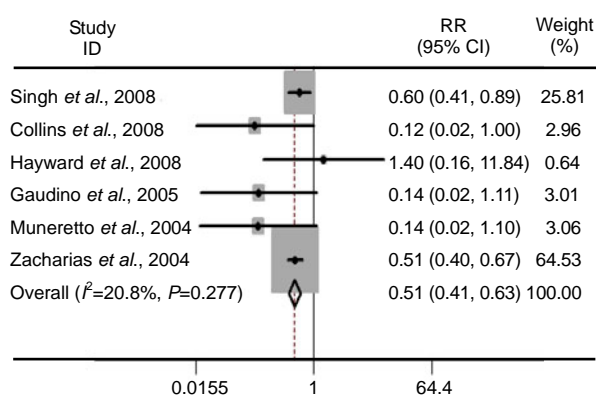


Fig. 1 Forest plot showing results from meta-analyses of trials reporting graft occlusion after coronary artery bypass with radial arteries compared to great saphenous veins

RR: relative risk; CI: confidence interval

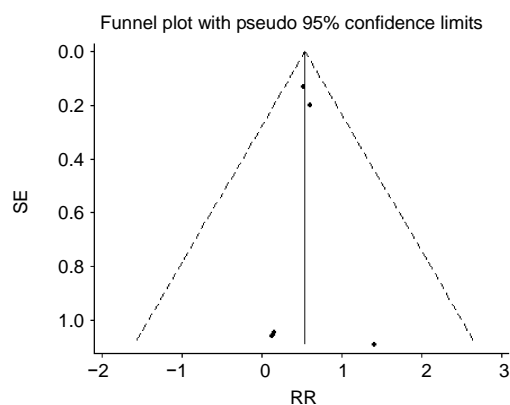


Fig. 2 Publication biases of all clinical studies reporting graft occlusion

RR: relative risk; SE: standard error

2. Harvest site infection

Four clinical trials, focusing on harvesting wound infections, demonstrated that there were significantly higher infection rates in legs (vein grafts) than in arms (radial artery grafts). Random effects (DerSimonian-Laird) pooled RR was 0.140 (95% CI 0.051–0.385, $P < 0.05$). Heterogeneity was significant ($I^2 = 59.8\%$) (Fig. 3), but without bias ($P = 1$).

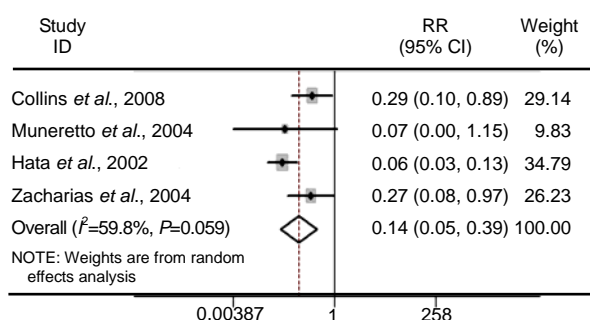


Fig. 3 Forest plot showing results from meta-analyses of trials reporting graft harvest site infection after coronary artery bypass with radial arteries compared to great saphenous veins

RR: relative risk; CI: confidence interval

3. Mortality

There were four studies reporting mortality after CABG, among which three were randomized trials, with follow-up ranging from one to six years. This systematic assessment demonstrated comparable mortality in the follow-up period between the two grafts (7.19% with radial artery graft vs. 8.55% with great saphenous vein graft; RR 0.839, 95% CI 0.661–1.065; no statistical heterogeneity, $P=0.927$) (Fig. 4).

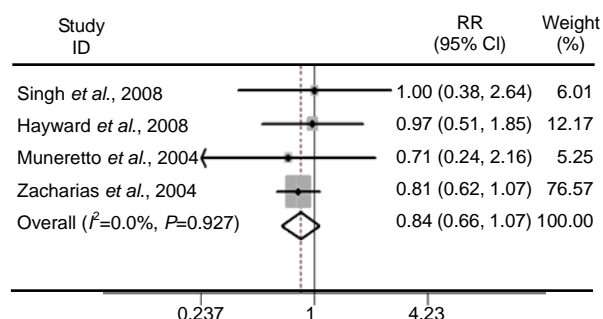


Fig. 4 Forest plot showing results from meta-analyses of trials reporting all cause mortality after coronary artery bypass with radial arteries compared to great saphenous veins

RR: relative risk; CI: confidence interval

3.3.2 Comparison between radial and right internal thoracic artery grafts

We only retrieved five published studies of four clinical controlled trials comparing the effects of CABG with radial and right internal thoracic artery grafts; hence the data available that could be pooled in the meta-analysis were limited. The pooling results showed comparable mortality and repeat percutaneous transluminal coronary angioplasty operatively (RR 0.68, 95% CI 0.36–1.28; RR 1.01, 95% CI 0.33–3.10). However, there may have been less cardiac-related

events (myocardial infarction, heart failure, etc.) in the radial artery group than in the right internal thoracic artery group (RR 0.49, 95% CI 0.28–0.87, $P=0.014$).

3.4 Sensitivity analysis results

We did not identify any significant difference in RR and heterogeneity for the outcomes of interest using both random and fixed effects models. Results in the graft occlusion risk from a random effects model were similar, with an RR of 0.507 (95% CI 0.369–0.696, $P<0.05$) and no statistical heterogeneity ($P=0.282$). When the matched trial was excluded, with only the five randomized studies in consideration for subgroup analysis, the RR was 0.496 (95% CI 0.347–0.709, $P<0.05$) without significant heterogeneity ($P=0.172$).

4 Discussion

The great saphenous vein graft has been used in coronary artery bypass surgery for several decades since the advent of CABG; however, radial artery grafting has become increasingly popular in a wide range of surgical specialties recently. Diabetes, emerging to be an epidemic as one of the major causes of coronary heart disease, increases the risk of vein graft failure. Sharing some main common favorable features with the left internal thoracic artery, such as arterial thick muscular wall and endothelial responsive vasodilatation, the radial artery is assumed to be of superiority over the great saphenous vein. In addition, there is less concern about sternal wound healing compared to using bilateral internal thoracic arteries.

The pooling results from this analysis in comparing radial artery with great saphenous vein grafts in coronary artery bypass suggest that radial artery grafts produce a less definitive graft occlusion in the early and middle terms. Possible explanations for this outcome may be as follows. First and foremost, the radial artery shares the intrinsic characteristics of a coronary artery, ensuring the constant blood flow with the coronary artery, including the function of vasodilatation, allowing modulation in supply volume, the distinct endothelial resistance to atherosclerosis, and the large scale of the arterial blood shear forces. In addition, there is more biocompatibility in the artery-artery anastomosis, which is the most frequent site producing thrombus. Last, but not least, the

superiority of radial-artery grafts may be attributed to more adaptability to the coronary vessel bed via autonomic regulation and neural-humoral response. On the other hand, the great saphenous vein graft, with a larger lumen compared to the native coronary artery in general, in addition to the presence of valves, might demonstrate flow characteristics different from that in the coronary artery. With regard to the post surgery mortality, no controlled study showed an encouraging outcome for the radial artery graft at the longest follow-up of eight years, and thus we relied on a pooling result. The discrepancy between radial artery patency and survival observed in most of the trials exists for many reasons, among which the predominant is the progressive lesions of the myocardium and transduction system contributed to by ischemia. More exactly, at a certain stage of coronary disease, ischemic related damage, such as myocardial fibrosis and transduction band abnormality, cannot be reversed in spite of reflow. Nevertheless, this does not suggest that randomly choosing arterial and venous grafts is wise. On the contrary, the characteristics of patients going through operation should be taken into consideration. Therefore, a randomized clinical trial focusing on longer-term survival rates of radial-artery and saphenous-vein coronary surgery is necessary.

In addition to the steadily increasing use of the radial artery as a coronary bypass graft, there is encouraging data regarding another arterial graft source. Improved survival rates with bilateral internal mammary artery grafts were obtained from a meta-analysis by Taggart *et al.* (2001). According to our pooling results, there was no significant difference in mortality between the two grafts. Meanwhile, survival estimates at 18 months and 6 years for patients who received radial and right internal thoracic artery grafts were comparable (Caputo *et al.*, 2003; Hayward *et al.*, 2007), in spite of a Cox regression model showing a stronger protective effect of the radial artery graft. This discrepancy might be due to the inclusive population bias existing in Taggart *et al.* (2001)'s report, because no randomized trial was included. However, there might be less cardiac-related events in the radial artery group, as suggested by our analysis. Whether the cardiac events originated from the study graft or not remains unclear. Unfortunately, only one trial (Hayward *et al.*, 2010) presented the outcomes of angiography. In terms of the inadequate and poor quality trials, long-term randomized trials are required to confirm the results of radial artery relative to right internal mammary artery

(RIMA) conduits.

To our knowledge, this is the first systematic analysis based on control clinical trials to report substantial graft failure reduction associated with radial artery use in non-LAD. Although a number of these describing the effect of CABG with radial artery on the risk of graft occlusion have discussed, and the consistent advantageous patency of radial artery grafts has also been described in a literature review (Georghiou *et al.*, 2005). However, there were still some details existing in the study inclusion deserving our consideration. To start with, no research particularly matched patients for diabetes, focusing on the occlusion rate in the impact of hyperglycemia between the two grafts. There was only one article indirectly analyzing the impact of diabetic status on CABG patency with multivariable regression. In addition, as with any mini-vascular surgery, the learning curve effect for mini-lumen anastomosis should be clarified, since graft patency rate and all-cause mortality will in the end be influenced. Finally, double blinding in the study may be impossible for the surgeon.

Due to data limitations, a further sub-analysis aiming to clarify the effects of different basic characteristics or concomitances in patency rates is in vain. However, the enrolled control trials all balanced the patients' baseline characteristics with no significant differences between groups in the proportion of diabetes. In addition, in spite of best efforts made to choose clear outcomes, bias in criterion-defining of events still could not be avoided. Taking the infection of graft harvest sites as an example, the pooling result suggested a reduction in infection rate, demonstrating a significant heterogeneity. This might be attributed to the different definitions of infection. In addition, publication bias should be always kept in mind. It is difficult to obtain complete raw data for some trials, i.e., the Australia Radial Artery Study (ARAS).

The new concept of arterial grafts has challenged the use of great saphenous vein grafts. It is assumed that the radial artery is probably the second best choice for a graft because of the arterial baseline characteristics, which is also confirmed by a handful of observational trials (Tatoulis *et al.*, 2009). And some randomized control studies recently showed reduced graft failure and less mortality relative to great saphenous vein. On the other hand, this superiority in occlusion rate failed to be demonstrated in terms of the radial artery patency and clinical outcomes. Simultaneously, improved survival in two

internal thoracic artery grafts has been reported, and the right internal thoracic artery could be the most obvious alternative as an arterial graft. Hence, our meta-analysis has come when the evidence comparing CABG with radial artery and other conduits is available; furthermore, each interventional effect can be measured quantitatively. Therefore, we provide a recommendation based on the evidence available, and this provides a guideline for clinical practice as well as an indication of the need for further clinical outcome studies.

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