Angiographic outcomes of radial artery versus saphenous vein in coronary artery bypass graft surgery: A meta-analysis of randomized controlled trials

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Introduction: The efficacy of coronary artery bypass graft (CABG) surgery for patients with ischemic heart disease is dependent on the patency of the selected conduit. The left internal thoracic artery is considered to be the best conduit for CABG. However, the preferred conduit between the radial artery (RA) and saphenous vein (SV) remains controversial. The present meta-analysis aims to establish the current level IA evidence on patency outcomes comparing the RA and SV.

Methods: Electronic searches were performed using 6 databases from their inception to March 2012. Two reviewers independently identified all relevant randomized controlled trials (RCTs) comparing patency outcomes of RA and SV grafts after CABG. Data were extracted and meta-analyzed according to angiographic end points at specified follow-up intervals.

Results: Five relevant RCTs were identified for inclusion in the present meta-analysis. Angiographic results indicated that the RA was significantly more likely to be completely patent and less likely to be associated with graft failure or complete occlusion at 4 years' follow-up and beyond. However, the RA was significantly more likely to be associated with string sign at 1 year of follow-up.

Conclusions: While acknowledging the limitations of heterogeneous surgical techniques, results from the present meta-analysis suggest potential superiority of the RA compared with the SV at midterm angiographic follow-up. However, the increased incidence of string sign associated with the RA is of potential clinical concern. Further research should be directed at correlating angiographic findings of string sign and graft failure to clinical symptoms and major adverse cardiac and cerebrovascular events at long-term follow-up. (*J Thorac Cardiovasc Surg* 2013;146:255-61)

Coronary artery bypass graft (CABG) surgery remains the gold standard treatment strategy for patients with left main coronary artery disease and multivessel disease.^{1,2} The efficacy of CABG is dependent on the long-term patency of the selected conduits. The left internal thoracic artery is established as the best conduit for CABG, particularly for grafting the left anterior descending artery.³ After initially unfavorable outcomes,⁴ there has been an emerging and renewed enthusiasm for the radial artery (RA) as an alternative conduit through the use of improved harvesting techniques and antispasmodic medications.⁵

Although a number of retrospective studies have indicated encouraging patency outcomes for RAs,⁶⁻⁸ there

remains a lack of consistent and robust clinical data to compare the RA to the saphenous vein (SV) for patients who undergo CABG. Proponents of total arterial revascularization highlight the superior clinical and angiographic results using the RA⁹ whereas sceptics report poor outcomes from large retrospective studies.¹⁰ The present meta-analysis aims to provide level IA evidence for the comparison of angiographic outcomes in RA versus SV conduits for CABG.

PATIENTS AND METHODS

Literature Search Strategy

Electronic searches were performed using Ovid MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, ACP Journal Club, and Database of Abstracts of Review of Effectiveness from their date of inception to March 2012. Only randomized controlled trials (RCTs) were included in the present meta-analysis, as recommended by the Centre for Evidence Based Medicine guidelines to provide the highest level of clinical evidence.¹¹ To achieve the maximum sensitivity of the search strategy and identify all studies, we combined the terms "radial artery" with "randomized controlled trial" as both keywords and MeSH headings. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. All relevant articles identified were assessed with application of the inclusion and exclusion criteria.¹²

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CI	= confidence interval
OR	= odds ratio
RA	= radial artery
RCT	= randomized controlled trial
SV	= saphenous vein
TIMI	= Thrombolysis in Myocardial Infarction

Selection Criteria

Eligible RCTs for the present meta-analysis included those in which patients with coronary artery disease underwent CABG using RAs and/or SVs and assessed angiographically for patency. When centers have published duplicate trials with accumulating numbers of patients or increased lengths of follow-up, only the most updated reports were included for qualitative appraisal at each time interval. To maintain the consistency of measured end points, the chief investigators of this study discussed angiographic definitions of "graft failure" before data analysis. It is acknowledged that patient selection for revascularization varied among institutions and sometimes within an institution at different time periods. All publications were limited to human subjects. Non-English articles were not excluded. Abstracts, case reports, conference presentations, editorials, and expert opinions were excluded. Review articles were omitted owing to potential publication bias and possible duplication of results.

Data Extraction and Critical Appraisal

All data were extracted from article texts, tables, and figures. When insufficient data were available from publications, corresponding authors were contacted to provide additional records. Two investigators independently reviewed each retrieved article. Assessment of risk of bias for each selected study was also independently performed by 2 investigators according to the most updated Cochrane statement.¹³ Discrepancies between the 2 reviewers were resolved by discussion and consensus. The final results were reviewed by the senior investigators.

Statistical Analysis

Meta-analysis was performed by combining the results of reported angiographic incidences of complete occlusion, string sign, graft failure, and complete patency. The odds ratio (OR) was used as a summary statistic. In the present study, both fixed- and random-effect models were tested. In a fixed-effects model, it was assumed that treatment effect in each study was the same, whereas in a random-effects model, it was assumed that there were variations between studies and the calculated ratios thus had more conservative value.¹⁴ χ^2 Tests were used to study heterogeneity between

trials. I^2 statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance. I^2 can be calculated as: $I^2 = 100\% \times (Q - df)/Q$, with Q defined as Cochrane's heterogeneity statistics and df defined as degree of freedom.¹⁵ An I^2 value of greater than 50% was considered substantial heterogeneity. If there was substantial heterogeneity, the possible clinical and methodologic reasons for this were explored qualitatively. In the present meta-analysis the results using the random-effects model were presented to take into account the possible clinical diversity and methodologic variation between studies. Specific analyses considering confounding factors were not possible because raw data were not available. All P values were 2-sided. All statistical analysis was conducted with Review Manager Version 5.1.2 (Cochrane Collaboration, Software Update, Oxford, United Kingdom).

RESULTS

Quantity and Quality of Trials

A total of 512 references were identified through the 5 electronic database searches. After exclusion of duplicate or irrelevant references, 43 potentially relevant articles were retrieved. After detailed evaluation of these articles, 21 studies remained for assessment. Manual search of the reference lists did not identify any additional relevant studies. After applying the selection criteria, 5 RCTs were selected for analysis. The study characteristics of these trials are summarized in Table 1. In these 5 studies, 1840 patients were randomized with 1708 angiographic results available for analysis to compare RA ($n = 859$) versus SV (849) conduits in CABG. Surgical details and baseline characteristics are summarized in Tables 2 and 3, respectively.

The 5 RCTs were assessed qualitatively using tools designed to measure the risk of bias, as recommended by the Cochrane collaboration. A summary of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias identified in each individual RCT is presented in Figures 1 and 2.

Assessment of Complete Occlusion

Complete occlusion was not significantly different between the RA and SV at 12 months' angiographic follow-up (9.1% vs 12.7%; OR, 0.71; 95% confidence interval [CI], 0.43-1.16; $P = .15$; $I^2 = 51\%$). However, beyond 4 years, the RA was found to be associated with a significantly lower risk for complete occlusion (2.7% vs 14.7%; OR,

TABLE 1. Summary of study characteristics of RCTs comparing RA versus SV as conduits for CABG surgery

First author	Year of publication	Country	Study period	No. randomized	No. analyzed	RA	SV	Angiographic follow-up (mo)	Primary end point
Desai ¹⁶	2004	Canada/NZ	1996-2001	561	440	440	440	8-12	Graft occlusion
Gaudino ¹⁷	2005	Italy	1994-1997	120	80	40	40	52	Graft patency
Collins ¹⁸	2008	UK	1998-2000	147	103	59	44	67	Graft occlusion
Hayward ¹⁹	2011	Australia	1996-2004	255	110	51	59	66	MACE
Goldman ²⁰	2011	US	2003-2009	757	535	269	266	2-24	Graft patency

RCT, Randomized controlled trial; RA, radial artery; SV, saphenous vein; CABG, coronary artery bypass grafting; NZ, New Zealand; UK, United Kingdom; US, United States; MACE, major adverse cardiac events, including mortality, myocardial infarction and repeat revascularisation.

TABLE 2. Summary of surgical techniques and grafted vessels in RCTs comparing RA versus SV as conduits for CABG surgery

First author	Native coronary artery stenosis	Territory grafted	Elective CABG	Surgical technique
Desai ¹⁶	>70% proximal lesion	RCA or LCx	67%	NR
Gaudino ¹⁷	>70% proximal lesion; >1 mm	OM1	100%	On pump 100%
Collins ¹⁸	>70% proximal lesion	LCx	100%	On pump 100%
Hayward ¹⁹	>70% proximal lesion; >1.5 mm	Best coronary after LAD	71% RA, 81% SV	On pump 100%
Goldman ²⁰	>70% proximal lesion	Determined by surgeon	100%	On pump 88%

RCT, Randomized controlled trial; RA, radial artery; SV, saphenous vein; CABG, coronary artery bypass grafting; RCA, right coronary artery; LCx, left circumflex artery; OM1, first oblique marginal branch; LAD, left anterior descending artery; NR, not reported.

0.17; 95% CI, 0.06-0.51; $P = .002$; $I^2 = 0\%$). The results beyond 4 years are summarized in Figure 3.

Assessment of String Sign

Angiographic finding of string sign was significantly higher in the RA group than in the SV group at 12 months' follow-up (7.4% vs 1.0%; OR, 7.97; 95% CI, 3.60-17.68; $P < .00001$; $I^2 = 0\%$), as well as a trend toward a higher incidence at beyond 4 years' follow-up (2.7% vs 0%; OR, 3.55; 95% CI, 0.57-22.11; $P = .17$; $I^2 = 0\%$). The results at 1 year are summarized in Figure 4.

Assessment of Graft Failure

Graft failure from each individual RCT included patients who had RA or SV grafts that were either completely occluded or had the string sign at the time of the follow-up angiography.¹⁶⁻²⁰ In addition, patients who had angiographic reports of Thrombolysis in Myocardial Infarction (TIMI) flow of 1 to 2,¹⁶ those with compromised flow state of more than 50%,¹⁸ stenosis of more than 80%,¹⁹ or stenosis of more than 75%²⁰ were also categorized as having failed grafts. It is acknowledged that the angiographic end points and methodology varied among institutions.¹⁶⁻²⁰ However, according to the aforementioned definitions, graft failure was similar between the RA and SV at 12 months (18.4% vs 15.5%; OR, 1.26; 95% CI, 0.78-2.03; $P = .34$; $I^2 = 65\%$) but significantly less likely in patients who had RA beyond 4 years' follow-up (6.0% vs 17.5%; OR, 0.31; 95% CI, 0.14-0.68; $P = .004$; $I^2 = 0\%$). These results are summarized in Figure 5.

Assessment of Complete Patency

Although complete graft patency was found to be similar between the RA and SV groups at 1 year (79.2% vs 82.5%;

OR, 0.79; 95% CI, 0.50-1.26; $P = .33$; $I^2 = 66\%$), the RA was more likely to result in a completely patent graft than was the SV beyond 4 years (89.9% vs 63.1%; OR, 5.19; 95% CI, 2.35-11.47; $P < .0001$; $I^2 = 0\%$). The results beyond 4 years are summarized in Figure 6.

DISCUSSION

Carpentier and associates⁴ first described the use of the RA in aorta-to-coronary artery bypass grafting in 1973 by reporting the short-term outcomes of 40 grafts in 30 patients. The advantages of the RA compared with the SV were duly noted, including the arterial structure, elasticity, and regularity of the lumen. However, the RA as an alternative conduit was largely abandoned for decades owing to concerns about spasm, early occlusion, and competitive flow. Since then, an improved understanding of the natural history of histologic changes in venous and arterial grafts and pharmacologic implications of antispasmodic drugs has culminated in a revival of the RA in the 1990s.^{5,21,22} In addition, revelation of the significant attrition rate of the SV conduit has further encouraged the exploration of arterial conduits.²³ Despite enthusiasm for total arterial revascularization from some centers, uncertainty regarding the superiority of the RA compared with the SV used in conventional CABG has prevented the widespread acceptance of the RA as a preferred conduit.^{10,24,25} A lack of consensus among clinicians is partly reflected by the fluctuating use of the RA for isolated CABG from 12.3% in 2002 to 5.5% in 2009 according to The Society of Thoracic Surgeons database.²⁶

Benedetto and associates²⁷ performed a meta-analysis of RCTs from 4 centers comparing the RA and SV using graft failure as the sole end point. This study did not include a recent RCT involving the largest number of participants to

TABLE 3. Summary of patient baseline characteristics of RCTs comparing RA versus SV as conduits for CABG surgery

Study	Age (y)		Female		Diabetes mellitus		Hypertension		Current smoker		Previous MI	
	RA	SV	RA	SV	RA	SV	RA	SV	RA	SV	RA	SV
Desai ¹⁶	61		57%		26%		46%		17%		46%	
Gaudino ^{17*}												
Collins ¹⁸	58	58	3%	5%	19%	14%	58%	50%	17%	5%	51%	45%
Hayward ¹⁹	73	73	20%	14%	29%	39%	47%	61%	73%†	71%†	NR	NR
Goldman ²⁰	61	62	1%	1%	42%	42%	79%	79%	23%	27%	40%	39%

RCT, Randomized controlled trial; RA, radial artery; SV, saphenous vein; CABG, coronary artery bypass grafting; MI, myocardial infarction. *No specific data available for RA and SV groups. †Ever smokers.

FIGURE 1. Methodologic quality graph summarizing the risk of bias from randomized controlled trials comparing radial artery versus saphenous vein for coronary artery bypass graft surgery.

date,²⁰ and it did not stratify patency outcomes according to different follow-up intervals. The authors concluded that the RA and SV had similar graft failure rates but were criticized for their methodology.²⁸ More recently, Athanasiou and associates performed a thorough systematic review

and meta-analysis of all randomized and nonrandomized studies comparing the RA and SV, citing the inadequacy of including only RCTs. This meta-analysis grouped RCTs with retrospective observational studies, some of which had controversial study designs and outcomes.^{10,29} The present meta-analysis aimed to assess the level IA clinical evidence of the RA versus the SV using multiple angiographic patency end points at specified time intervals according to recommended guidelines.¹¹

Results of the present meta-analysis indicate that the RA does not appear to be superior to the SV at 1 year of follow-up, and indeed it is more likely to be associated with the string sign, which is generally considered to be a form of graft failure.³⁰⁻³² However, the RA has significantly superior angiographic patency outcomes compared with the SV at 4 years and beyond, according to end points of complete graft occlusion, graft failure, and complete patency. Heterogeneity assessment of these long-term studies revealed a low degree of heterogeneity ($I^2 = 0\%$) in all measured outcomes. Overall, our findings are consistent with previous observational studies that report superior outcomes from total arterial revascularization compared with conventional CABG using venous conduits, which becomes more evident on longer follow-up.²³

The significance of the angiographic string sign has long been recognized, not only in conduits used in CABG but for other systemic vascular diseases.³³ Miwa and associates³⁴ retrospectively analyzed their data from the Radial Artery Patency Study (RAPS) trial,¹⁶ which identified string sign in 31 of 440 RA and 4 of 440 SV grafts ($P = .001$). In their study, string sign was defined a priori as a patent graft that was diffusely narrowed, with a diameter less than 1 mm. It was further categorized as “complete” if the narrowing was along the full length of the graft or “partial” if only a segment was affected. Although the results of this study clearly demonstrated a preponderance for string signs in RA grafts, especially in patients with less than 90% narrowing of the native coronary artery, the clinical impact of this angiographic phenomenon was less clear. Clinical findings of

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Collins	+	+	+	+	+	-
Desai	+	+	+	+	+	+
Gaudino	+		+	+	+	-
Goldman	+		+	-	+	+
Hayward	+	+	+	-		

FIGURE 2. Methodological quality summary of randomized controlled trials comparing radial artery versus saphenous vein for coronary artery bypass graft surgery.

FIGURE 3. Forest plot of the odds ratio (OR) of complete occlusion beyond 4 years after using radial artery (RA) versus saphenous vein (SV) as a conduit during coronary artery bypass grafting. The estimate of the OR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number randomized is shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. *M-H*, Mantel-Haenszel.

angina appeared to correlate more with TIMI flow rather than the string sign itself. Furthermore, there was no significant difference in the incidence of myocardial infarction between patients who had string signs compared with those who did not, although the authors acknowledged limitations owing to their relatively small sample size. Certainly, the nonlinear correlation between TIMI flow and the incidence of string sign suggests the cause may be multifactorial, such as competitive collateral flow, translesional flow through a small target artery, poor harvesting technique, or inherent graft disease.^{30,31} Nonetheless, results from the present study warrant further prospective studies that examine the correlation of the string sign from RA conduits to potentially significant clinical end points.

A number of limitations should be acknowledged about the present study, and the results should be interpreted with caution. First, patients from the RCTs included in the present meta-analysis are a highly selected cohort who underwent isolated CABG. Specifically, all patients had to have a greater than 70% proximal lesion in the native coronary vessel, inasmuch as it has been established that patients with lower-grade lesions had an increased propensity for competitive flow and were probably not suitable or ethical for randomization.¹⁶⁻²⁰ Second, graft patency is

dependent on a number of important variables. These include the type of conduit used, size of the native coronary artery, the severity and location of disease, the territory of the runoff, the surgical technique and experience of the surgeon, and perioperative use of antispasmodic medications, all of which differed among studies. This may partly explain the heterogeneity identified between the 2 large RCTs conducted by Desai,¹⁶ Goldman,²⁰ and their associates, the latter of which included a significant proportion of patients who underwent off-pump CABG. However, owing to the randomization process, confounding factors were minimized within each individual study, and the present meta-analysis represents a summary of the highest level of evidence in the current literature.

In view of our findings, we conclude that the RA offers better midterm angiographic patency outcomes than does the SV for selected patients with severe proximal lesions in the setting of multivessel disease. However, their likelihood of causing the string sign and the lack of clear evidence on clinical end points such as major adverse cerebrovascular and cardiac events warrants further randomized studies with longer follow-up and measurement of clinical outcomes. Future trials should also assess

FIGURE 4. Forest plot of the odds ratio (OR) of string sign angiographic finding at 1 year after using radial artery (RA) versus saphenous vein (SV) as a conduit during coronary artery bypass grafting. The estimate of the OR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number randomized is shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. *M-H*, Mantel-Haenszel.

FIGURE 5. Forest plot of the odds ratio (OR) of graft failure beyond 4 years after using radial artery (RA) versus saphenous vein (SV) as a conduit during coronary artery bypass grafting. The estimate of the OR of each trial corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number randomized is shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the *solid diamonds*. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. *M-H*, Mantel-Haenszel.

FIGURE 6. Forest plot of the odds ratio (OR) of complete patency beyond 4 years after using radial artery (RA) versus saphenous vein (SV) as a conduit during coronary artery bypass grafting. The estimate of the OR of each trial corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number randomized is shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the *solid diamonds*. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. *M-H*, Mantel-Haenszel.

potential differences in costs and quality of life that are not apparent on short-term follow-up.³⁵

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