Systematic Review

A meta-analysis of randomized controlled trials on mid-term angiographic outcomes for radial artery versus saphenous vein in coronary artery bypass graft surgery

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Background: Currently, saphenous vein (SV) and radial artery (RA) are the most commonly used conduits in combination with the left internal mammary artery for conventional coronary artery bypass graft surgery (CABG). The present meta-analysis aimed to assess the existing evidence from randomized controlled trials (RCTs) to compare the angiographic outcomes of these two conduits at mid-term follow-up.

Methods: Four relevant and updated RCTs with follow-up beyond 3 years were identified using five electronic databases. Angiographic endpoints included complete occlusion, 'string sign', graft failure and complete patency.

Results: The incidence of complete occlusion was significantly lower after using RA compared to SV [6.7% *vs*. 17.2%; odd ratio (OR), 0.36; 95% confidence interval (CI), 0.23-0.58; P<0.0001]. The angiographic 'string sign' was significantly more likely to be identified after using RA compared to SV (3.1% *vs*. 0%; OR, 5.65; 95% CI, 1.21-26.39; P=0.03). Graft failure was significantly lower after RA compared to SV (9.6% *vs*. 18.8%; OR, 0.47; 95% CI, 0.30-0.72; P=0.0005). Complete graft patency was found to be significantly higher after RA compared to SV (88.6% *vs*. 75.8%; OR, 3.19; 95% CI, 1.42-7.16; P=0.005).

Conclusions: Results of the present meta-analysis suggest that selected patients with severe, proximal stenosis may have superior angiographic outcomes at mid-term follow-up after using RA compared to SV for CABG. However, RA is associated with a significantly higher incidence of the 'string sign'. Future studies should aim to collect additional data on symptomatic outcomes.

Keywords: Meta-analysis; radial artery (RA); saphenous vein (SV); coronary artery bypass graft surgery (CABG); conduits

Submitted Jun 22, 2013. Accepted for publication Jul 08, 2013.
doi: 10.3978/j.issn.2225-319X.2013.07.03
Scan to your mobile device or view this article at: http://www.annalscts.com/article/view/2400/3266

Introduction

For selected patients with severe coronary artery disease, coronary artery bypass graft surgery (CABG) remains the superior management approach compared to percutaneous coronary interventions (1,2). The left internal mammary artery (LIMA) has long been established as the preferred conduit with the lowest long-term attrition rate, and is often selected for grafting the left anterior descending artery in conventional CABG (3,4). Conduit selection for the left circumflex and right coronary artery territories has been more variable amongst surgeons.

Currently, the saphenous vein (SV) and radial artery (RA) are the most commonly used conduits after LIMA for CABG. Although the use of RA was first reported in 1973 by Carpentier, it was not popularized until the 1990s,

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when antispasmodic medications and improved harvesting techniques were routinely used to prevent early spasm and occlusion (5). The use of SV was pioneered by Favaloro in the early years of CABG, but its early occlusion and long-term attrition rates have resulted in only half of all vein grafts being patent and without significant stenoses at 10-years (6,7). The aim of the present meta-analysis was to assess the existing evidence to compare mid-term angiographic outcomes of RA versus SV for CABG by using all available data from randomized controlled trials (RCTs).

Methods

Literature search strategy

Electronic searches were performed on Ovid Medline, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club and Database of Abstracts of Review of Effectiveness (DARE) from their dates of inception to March 2013. To assess the highest level of available evidence according to the Centre for Evidence Based Medicine (CEBM) guidelines, only RCTs were included in the present meta-analysis (8). The search strategy included a combination of 'radial artery' and 'randomized controlled trial' as either keywords or 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 predefined selection criteria.

Selection criteria

Selected RCTs for the present meta-analysis included those that provided data on comparative angiographic outcomes for RA and SV after CABG. When institutions have published duplicate trials, only the most updated reports were included for qualitative appraisal. Measured 'mid-term' outcomes were limited to studies with follow-up beyond 3 years, consistent with previous reports (9). It is acknowledged that patient and coronary territory selection for revascularization varied amongst institutions and sometimes within an institution at different periods. All publications were limited to human subjects and English language. Abstracts, case reports, conference presentations, editorials and expert opinions were excluded.

Data extraction and critical appraisal

Data were extracted from texts, tables and figures of selected RCTs. When insufficient or ambiguous data were presented from publications, corresponding authors were contacted to provide additional information. Two investigators (S.A. and K.W.) independently reviewed each retrieved article. Discrepancies between the two reviewers were resolved by discussion and consensus with the senior investigators (C.C. and T.D.Y.).

Statistical analysis

Meta-analysis was performed by combining the reported angiographic incidences of complete occlusion, 'string sign', graft failure and complete patency. The odds ratio (OR) was used as a summary statistic. χ^2 tests were used to study heterogeneity between trials. The I^2 index was used to estimate the percentage of total variation across studies, due to heterogeneity rather than chance. An I^2 value of greater than 50% was considered as substantial heterogeneity. If there was substantial heterogeneity, the possible clinical and methodological reasons for this were explored qualitatively. All P values were two-sided. All statistical analyses were conducted with Review Manager Version 5.1.2 (Cochrane Collaboration, Software Update, Oxford, UK).

Results

Quantity and quality of trials

A total of 521 references were identified through the five electronic database searches. After exclusion of duplicate references, 507 potentially relevant articles were retrieved. After detailed evaluation of these articles, 23 studies remained for assessment. After applying the selection criteria, four RCTs were selected for quantitative assessment and meta-analysis (10-13). The search strategy is summarized in *Figure 1*, and the study characteristics of the selected RCTs are summarized in *Table 1*. Overall, 1,078 patients underwent randomization prior to CABG, with 831 mid-term angiographic results to compare RA (n=419) versus SV (n=412) grafts. Patient baseline characteristics and the grafted coronary territories are summarized in *Table 2*.

Assessment of complete occlusion

The incidence of complete occlusion was significantly lower after using RA compared to SV [6.7% *vs*. 17.2%; OR, 0.36; 95% confidence interval (CI), 0.23-0.58; P<0.0001; I^2=0%],

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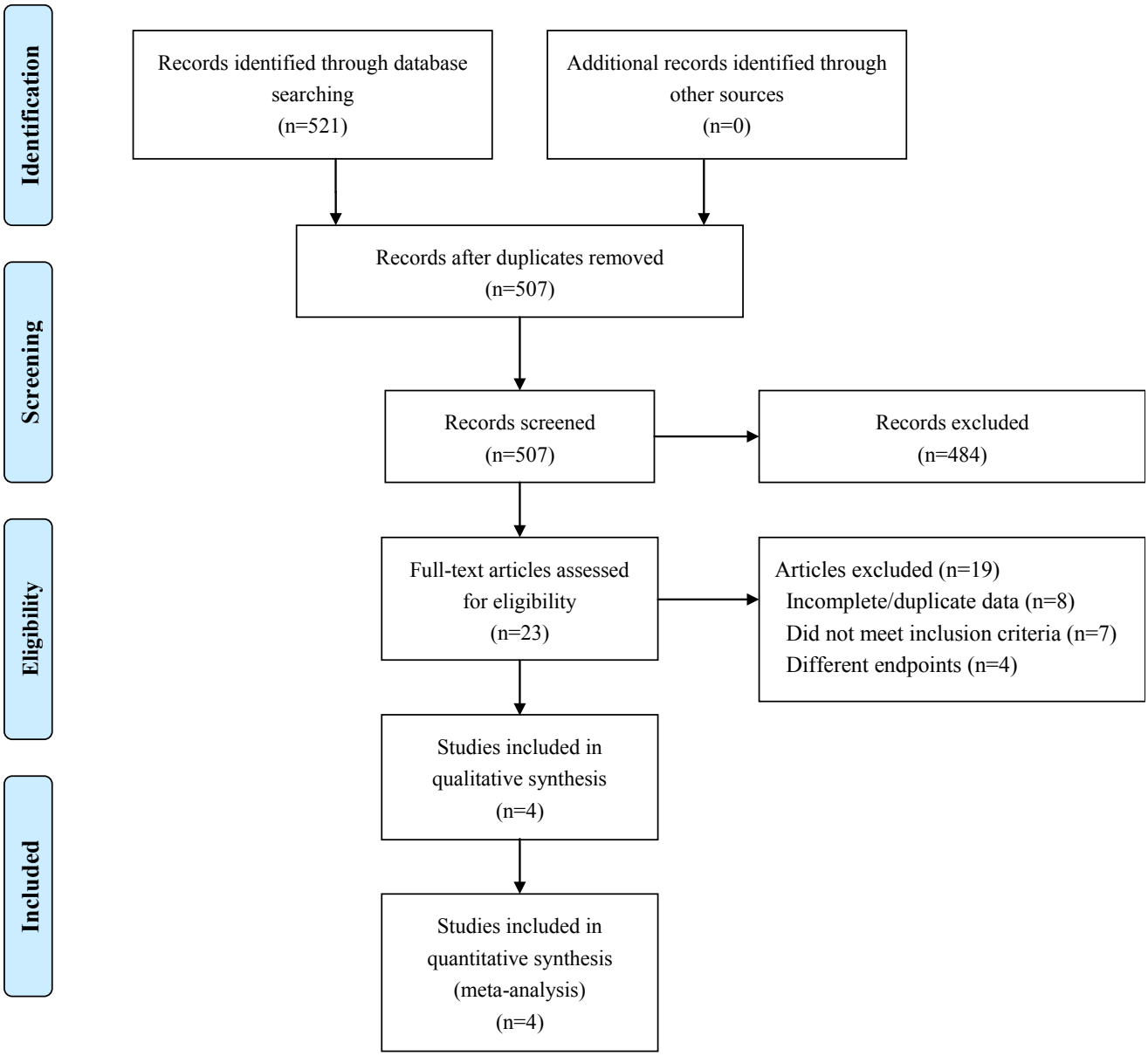

Figure 1 PRISMA chart summarizing the systematic review search

as summarized in *Figure 2*. The definition of 'complete occlusion' was consistent amongst trials.

Assessment of 'string sign'

The angiographic 'string sign' was significantly more likely to be identified after using RA compared to SV (3.1% *vs.* 0%; OR, 5.65; 95% CI, 1.21-26.39; P=0.03; I^2=0%), as summarized in *Figure 3*. The definition of the 'string sign' was not elaborated in detail but generally considered as 'severe diffuse graft narrowing' (11,14).

Assessment of graft failure

Graft failure was significantly lower after RA compared to SV (9.6% *vs.* 18.8%; OR, 0.47; 95% CI, 0.30-0.72; P=0.0005; I^2=0%), as summarized in *Figure 4*. The definition of graft failure included complete occlusion and 'string sign,' as well as patients who had compromised flow state of >50% (11), stenosis of >80% (12) and Thrombolysis

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Table 1 Summary of study characteristics of randomized-controlled trials comparing radial artery versus saphenous vein as conduits for coronary artery bypass graft surgery

Study	Year of publication	Country	Enrolment period	n randomized	n analyzed	RA	SV	Angiographic follow-up	Primary endpoint
Gaudino	2005	Italy	1994-1997	120	80	40	40	52 months	Graft patency
RSVP	2008	UK	1998-2000	142	103	59	44	67 months	Graft occlusion
RAPCO	2011	Australia	1996-2004	255	110	51	59	66 months	MACE
RAPS	2012	Canada	1996-2001	561	269*	269	269	92 months	Functional graft occlusion

RA, radial artery; SV, saphenous vein; MACE, major adverse cardiac events, including mortality, myocardial infarction and repeat revascularisation; *including 35 patients assessed by computed tomography angiography; RSVP, Radial artery versus Saphenous Vein Patency; RAPCO, Radial Artery Patency and Clinical Outcomes; RAPS, Radial Artery Patency Study

Table 2 Summary of patient baseline characteristics and territory grafted in selected randomized-controlled trials comparing radial artery versus saphenous vein as conduits for coronary artery bypass graft surgery

Study	Age (years)		Female		Diabetes mellitus		Hypertension		Territory grafted
	RA	SV	RA	SV	RA	SV	RA	SV	
Gaudino	NR	NR	NR	NR	NR	NR	NR	NR	1st oblique marginal
RSVP	58	58	3%	5%	19%	14%	58%	50%	Left circumflex
RAPCO	73	73	20%	14%	29%	39%	47%	61%	Best coronary after LAD
RAPS	60		15%		31%		45%		RCA or left circumflex

RA, radial artery; SV, saphenous vein; LAD, left anterior descending artery; RCA, right coronary artery; NR, not reported

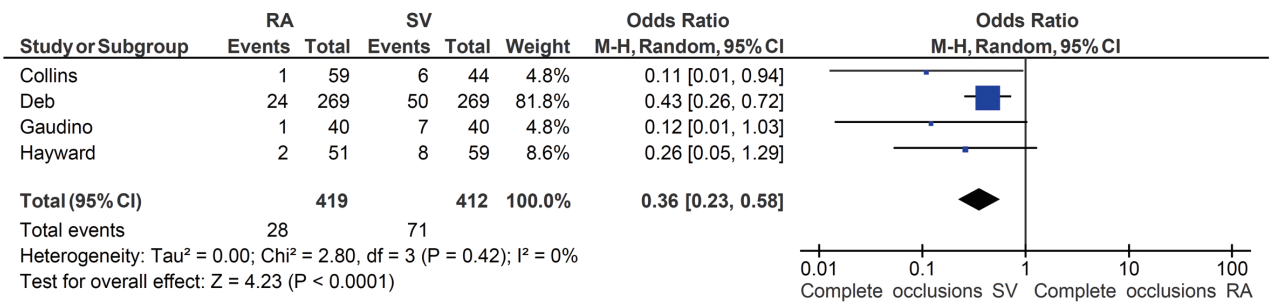

Figure 2 Forest plot of the odds ratio (OR) of complete occlusion at mid-term follow-up beyond 3-year after using radial artery (RA) versus saphenous vein (SV) as a conduit during coronary artery bypass grafting. The estimate of the OR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% CI. On each line, the number of events as a fraction of the total number randomized is shown for both treatment groups. 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

In Myocardial Infarction (TIMI) flow of 1-2 (13).

Assessment of complete patency

Complete graft patency, as defined by TIMI flow 3 (13) or 'perfect patency' (10,11), was found to be significantly higher after RA compared to SV (88.6% *vs*. 75.8%; OR, 3.19; 95% CI, 1.42-7.16; P=0.005; I^2=59%), as summarized in *Figure 5*. Complete patency was not reported in one trial (12).

Discussion

Selection of the appropriate conduit for patients undergoing CABG is of paramount importance to minimize mortality

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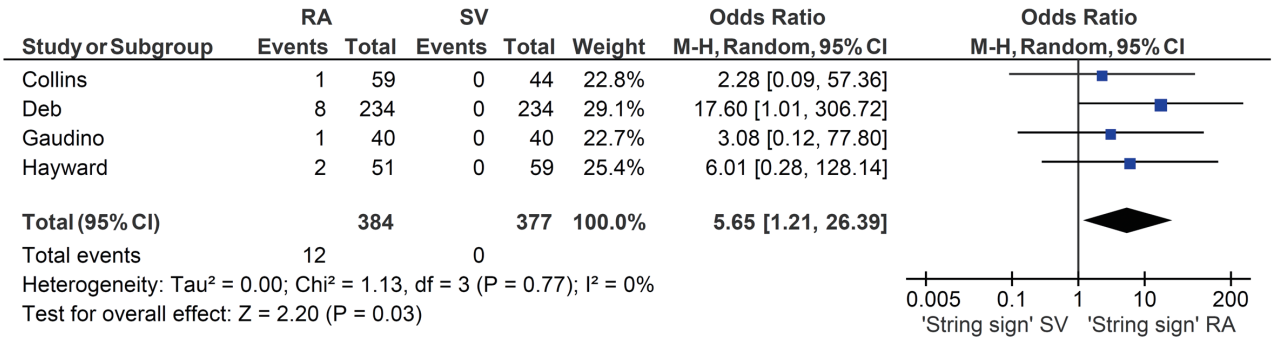

Figure 3 Forest plot of the odds ratio (OR) of angiographic 'string sign' at mid-term follow-up beyond 3-years after using radial artery (RA) versus saphenous vein (SV) as a conduit during coronary artery bypass grafting. The estimate of the OR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% CI. On each line, the number of events as a fraction of the total number randomized is shown for both treatment groups. 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

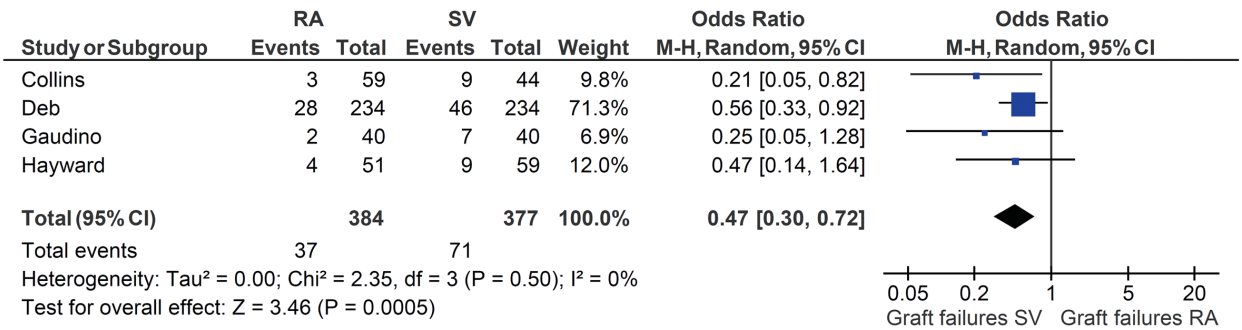

Figure 4 Forest plot of the odds ratio (OR) of graft failure at mid-term follow-up beyond 3-years after using radial artery (RA) versus saphenous vein (SV) as a conduit during coronary artery bypass grafting. The estimate of the OR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% CI. On each line, the number of events as a fraction of the total number randomized is shown for both treatment groups. 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

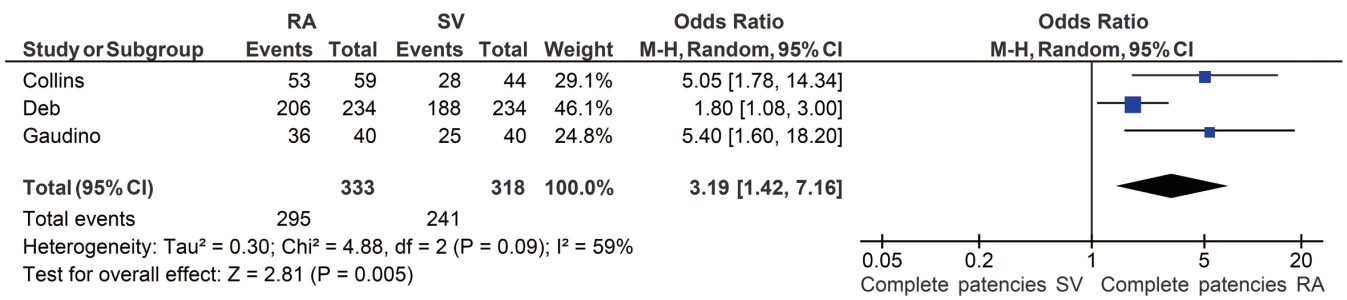

Figure 5 Forest plot of the odds ratio (OR) of complete patency at mid-term follow-up beyond 3-years after using radial artery (RA) versus saphenous vein (SV) as a conduit during coronary artery bypass grafting. The estimate of the OR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% CI. On each line, the number of events as a fraction of the total number randomized is shown for both treatment groups. 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

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and recurrence of symptoms. Additionally, the reduced need for repeat intervention remains a major advantage of CABG compared to PCI, especially for patients with severe coronary artery disease (2). The use of bilateral internal mammary arteries (BIMA) has been shown to confer a survival advantage for patients undergoing CABG (15,16). However, utilization of BIMA remains limited to a relatively low proportion of patients in the current clinical setting. The selection of SV or RA remains the most popular conduit choice for conventional CABG in combination with LIMA. However, observational data on mid-term clinical outcomes are conflicting, and the superiority of arterial conduits is not unanimously accepted by the cardiothoracic community (17).

The present systematic review identified four RCTs that presented data on angiographic outcomes of RA versus SV at follow-up beyond three years. Results of our meta-analysis demonstrated significantly higher incidences of graft failure and complete occlusion for SV, and significantly higher incidences of complete patency and the 'string sign' for RA at the time of the latest follow-up. These findings are consistent with large retrospective series, including a recent single-institutional study involving 1,851 patients that demonstrated significantly lower incidences of graft failure and higher incidences of patency for RA compared to SV (18). Similarly, a meta-analysis by Athanasiou and colleagues found that the RA was more likely to be patent at mid-term (1-5 years) (9). The superiority of RA angiographic outcomes may be partly explained by the differing pathophysiological process of venous and arterial atherosclerosis, with venous grafts being more likely to progress to concentric and diffuse lesions, that are vulnerable to rupture as a result of a less developed fibrous cap (19).

A number of limitations to our study should be acknowledged and interpretation of our results should not be generalized to all patients who undergo CABG. Firstly, it should be noted that patient selection and grafted territories differed between trials. However, all studies required eligible patients to demonstrate a minimum 70% proximal stenosis in their native coronary artery prior to randomization. This was partly because patients with less severe coronary artery disease are known to be more likely to suffer from graft failure and the effects of competitive flow, which has a more pronounced effect on arterial conduits (14,20). Secondly, it should be emphasized that angiographic endpoints and measurement systems differed between trials, with the primary endpoints ranging from graft patency (10), graft occlusion (11) and major adverse cardiac events (12). The Radial Artery Patency Study (RAPS) changed their primary endpoint from complete graft occlusion at 1-year (14) to functional graft occlusion beyond five years (13). Although the majority of data were derived from conventional angiograms, computed tomography angiograms were also employed in recent years to evaluate graft failures in this trial (13). These differences and the limited number of studies that presented data on complete patency may have contributed to the significant heterogeneity identified between trials. In addition, recent studies have suggested that specific subgroups such as male patients (21), elderly patients (22) and patients with diabetes mellitus (23) may derive more benefit from RA. It should be recognized that these potential prognostic factors differed significantly between trials, as summarized in *Table 2*, and may have influenced angiographic outcomes.

Ultimately, a multitude of factors relating to the conduit and the target coronary artery contribute to determining its long-term graft patency, including the selection of artery versus vein, harvesting technique, storage solution, as well as the size, severity of stenosis, and distal runoff of the native coronary artery (24). Using the available data from RCTs in the current literature, our meta-analysis suggests that radial arteries may be associated with superior angiographic outcomes compared to SV grafts for selected patients undergoing isolated CABG at mid-term follow-up. Future studies should correlate with clinical outcomes such as major adverse cardiac and cerebrovascular events and angina symptoms. Long-term follow-up data from the Veterans Affairs study may provide further robust data to compare RA and SV conduits (25). Novel surgical techniques such as endoscopic harvesting of conduits should also be examined.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Cao C, Ang SC, Wolak K, Peeceeyen S, Bannon P, Yan TD. A meta-analysis of randomized controlled trials on mid-term angiographic outcomes for radial artery versus saphenous vein in coronary artery bypass graft surgery. Ann Cardiothorac Surg 2013;2(4):401-407. doi: 10.3978/j.issn.2225-319X.2013.07.03

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