European Journal of Cardio-Thoracic Surgery 47 (2015) 59–65
doi:10.1093/ejcts/ezu111 Advance Access publication 30 March 2014

ORIGINAL ARTICLE

Cite this article as: Benedetto U, Raja SG, Albanese A, Amrani M, Biondi-Zoccai G, Frati G. Searching for the second best graft for coronary artery bypass surgery: a network meta-analysis of randomized controlled trials. Eur J Cardiothorac Surg 2015;47:59–65.

Searching for the second best graft for coronary artery bypass surgery: a network meta-analysis of randomized controlled trials†

Umberto Benedetto[a,*], Shahzad G. Raja[a], Alberto Albanese[a], Mohammed Amrani[a], Giuseppe Biondi-Zoccai[b] and Giacomo Frati[b,c]

[a] Department of Cardiac Surgery, Harefield Hospital, London, UK
[b] Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy
[c] Department of AngioCardio Neurology, IRCCS NeuroMed, Pozzilli, Italy

* Corresponding author. Department of Cardiac Surgery, Harefield Hospital, London, UK. Tel: +44-1895-828550; fax: +44-1895-828992; e-mail: umberto.benedetto@hotmail.com (U. Benedetto).

Received 25 September 2013; received in revised form 18 November 2013; accepted 17 December 2013

Abstract

OBJECTIVES: There is a lack of unequivocal evidence basis for selecting the best second conduit in coronary artery bypass grafting (CABG). We thus aimed to perform head-to-head relative effect estimate on angiographic outcomes for second conduits, including the right internal mammary artery (RIMA), radial artery (RA), right gastroepiploic artery (RGEA) and saphenous vein graft (SVG) by means of network meta-analysis of randomized controlled trials (RCTs).

METHODS: Databases were searched for RCTs comparing angiographic outcomes (≥4 weeks) of second conduits in CABG. Odds ratios (95% confidence intervals) were computed with Markov Chain Monte Carlo simulation.

RESULTS: A total of nine RCTs were identified, including 2780 patients and 1620 angiographic results available for analysis to compare RIMA (n = 145) versus RA (n = 871) versus RGEA (n = 92) versus SVG (n = 845). The mean time to angiographic follow-up ranged from 1 to 7.7 years. An SVG was significantly associated with a 4-fold (1.67–16.00) and 3-fold (0.78–22.20) increased risk of late (≥4 years) functional graft occlusion when compared with the RIMA and RA, respectively. A RIMA was associated with a non-significant 27% absolute risk reduction for functional graft occlusion when compared with the RA.

CONCLUSIONS: The present network meta-analysis consistently demonstrated an angiographic superiority of RIMA and RA over SVG. The RIMA is expected to achieve a better patency rate than the RA, but further studies are needed.

Keywords: Coronary disease • Coronary artery bypass grafting • Meta-analysis

INTRODUCTION

The long-term patency of conduits used is one of the most important variables in determining long-term outcomes after coronary artery bypass grafting (CABG) [1].

It has been well documented and demonstrated that the use of the left internal mammary artery (LIMA) to graft the left anterior descending (LAD) artery has significant benefits compared with using a saphenous vein graft (SVG) [1].

Unfortunately, we do not have an unequivocal evidence basis for selecting bypass conduits beyond great confidence in the superiority of LIMA grafted to the LAD artery. It was assumed that this inherent superiority of the LIMA over SVG would also be true of other arterial conduits such as the right internal mammary artery (RIMA) [2] the radial artery (RA) [3] and the right gastroepiploic artery (RGEA) [4]. These conduits can be safely procured and used for bypassing coronary arteries. However, this assumed inherent superiority of using any arterial conduit compared with using an SVG to targets other than the LAD artery has been much harder to prove. Although observation studies suggested a survival advantage of using second arterial conduits such as RA or RIMA instead of SVG [2, 3], the angiographic superiority of arterial conduits over SVG is still debated [5, 6].

Owing to the lack of a conclusive evidence supporting a superiority of arterial conduits over SVG and an unequivocal evidence basis for selecting the best second arterial conduit, arterial grafts aside from the LIMA are still largely underutilized [7].

Network meta-analysis (or Mixed Treatment Comparison, MTC) is a technique to meta-analyse more than two strategies at the same time. Using a full Bayesian evidence network, all indirect comparisons are taken into account to arrive at a single, integrated estimate of the effect of all included treatments based on all the available evidences. Their role in clinical research and practice has already been established [8].

† Presented at the 27th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Vienna, Austria, 5–9 October 2013.

We thus aimed to perform head-to-head relative effect estimate on angiographic outcomes for second conduits, including RIMA, RA, RGEA and SVG by means of network meta-analysis of randomized controlled trials (RCTs) to establish whether there is consistent evidence supporting an angiographic superiority from arterial conduits over SVG. Comparison among arterial conduits was also implemented to identify the second best arterial conduit.

MATERIALS AND METHODS

Design

The present review was performed according to the Cochrane Collaboration and PRISMA statements [9].

Search

MEDLINE/PubMed was searched according to this highly sensitive strategy on 10 September 2013: (radial artery OR right internal AND mammary artery OR right internal thoracic artery OR right gastroepiploic artery OR saphenous vein) AND (randomized controlled trial [pt] OR controlled clinical trial[pt] OR randomized controlled trials [mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR random*[tw] OR research design[mh:noexp] OR follow-up studies [mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw]) NOT (animal[mh]) NOT (comment [pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt])). In addition, Google Scholar, The Cochrane Library and Scopus were also searched for pertinent citations.

Selection

Study selection was performed by two independent reviewers (Umberto Benedetto and Alberto Albanese), with divergences resolved by consensus. Citations were first scanned at the title/abstract level. Shortlisted studies were then retrieved in full text.

Studies were included if: reporting on randomized trials, comparing angiographic patency of arterial conduits and/or SVG used as a second conduit to graft non-LAD targets. Studies were excluded if non-randomized and the angiographic patency was not undertaken or reported or the angiographic follow-up was undertaken within 4 weeks of surgery.

Abstraction and appraisal

Data abstraction and study appraisal were performed by two independent reviewers (Umberto Benedetto and Alberto Albanese), with divergences resolved by consensus. Study validity was appraised according to the risk of bias tool recommended by The Cochrane Collaboration. Key study and patient characteristics were extracted, including the following outcomes, reported at the longest available follow-up according to intention-to-treat principles:

Outcomes. Functional graft occlusion (primary end point) defined as the lack of thrombolysis in myocardial infarction flow grade 3, according to invasive angiography.

Complete graft occlusion (secondary end point) defined as the absence of visible opacification of the study graft despite aortogram (thrombolysis in myocardial infarction flow grade 0).

The occurrence of the string sign (defined as a severe diffuse graft narrowing) was also evaluated to compare RIMA versus RA angiographic outcomes in a pair-wise meta-analysis.

Analysis. Categorical variables are reported as events and were compared with odds ratios (ORs) with 95% confidence intervals. Direct comparisons from two or more trials were pooled in a pair-wise meta-analysis using the DerSimonian–Laird method. Variation in effect estimates beyond chance for the primary outcome was assessed by means of I^2. Thresholds for the interpretation of I^2 were as follows:

(i) 0–40%: might not be important;
(ii) 30–60%: may represent moderate heterogeneity;
(iii) 50–90%: may represent substantial heterogeneity;
(iv) 75–100%: considerable heterogeneity.

In the presence of significant variation in effect estimates, sensitivity analysis by means of meta-regression and subgroup analysis was performed to identify causes of heterogeneity among covariates including time to follow-up angiography, target vessel, type of randomization, mean age and prevalence of female gender. To investigate whether inference was driven from the evidence on single comparison, leave-one-out meta-analysis was performed in the presence of significant heterogeneity. Network meta-analyses were performed to determine the relative head-to-head effects of each conduit. Estimates of relative effects and all model parameters were obtained through Markov Chain Monte Carlo simulation from the posterior distributions. Four parallel Markov Chain Monte Carlo simulations were run for a burn-in period of 50 000 interactions, after which 50 000 interactions were saved for posterior summaries. Inconsistency of evidence, in addition to heterogeneity within a comparison, occurs when a treatment C has a different effect when it is compared with A or B. Node-splitting analysis was used to assess inconsistency.

If the analyses are performed within a Bayesian framework, the uncertainty in the relative effect estimates can be translated into probabilities of decision uncertainty. The Bayesian approach was, therefore, used to estimate the probability that each of the conduits is the best second conduit taking into account the primary study end point (functional graft occlusion). According to previous meta-analysis suggesting a better patency rate for arterial conduits only at longer term follow-up [5], a subanalysis was performed including only RCTs with an angiographic follow-up of ≥4 years.

All the analyses were conducted using R, version 2.15.2 (R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2012. http://www.R-project.org), and GeMTC package, version 0.4 (GertVam Valkenhoef, An R package for Mixed Treatment Comparison).

RESULTS

Studies

From a total of 381 citations, seven publications were finally identified [10–16]. Gaudino *et al.* [12] and Hayward and Buxton [15] conducted two independent trials that were part of the same study design. Therefore, the final analysis included a total of nine trials. Specifically, five trials compared RA versus SVG [10, 11,

14–16], two trials both from Gaudino *et al.* [12] compared RIMA versus RA versus SVG, one trial compared RIMA versus RA [15] and one trial compared RGEA versus SVG [13].

In these nine studies, 2780 patients were randomized with 1620 angiographic results available for analysis to compare RIMA ($n = 145$) versus RA ($n = 871$) versus RGEA ($n = 92$) versus SVG ($n = 845$) in CABG. The mean time to angiographic follow-up ranged from 1 to 7.7 years. Surgical details and baseline characteristics are summarized in Tables 2 and 3, respectively. Overall, six studies reported angiographic comparisons after a mean time follow-up of ≥4 years [10–12, 15, 16], with 794 angiographic results available for analysis to compare RIMA ($n = 145$) versus RA ($n = 506$) versus SVG ($n = 377$). Evidence networks of these trials are summarized in Fig. 1 and the study characteristics are summarized in Tables 1 and 2.

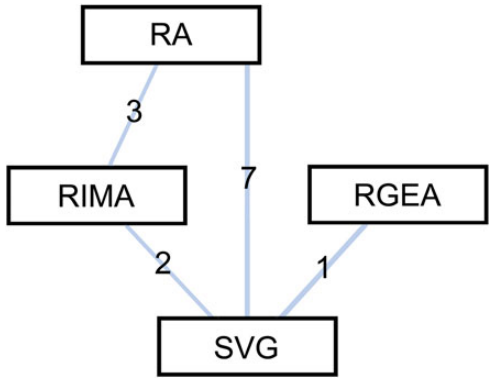

Figure 1: Network evidence. RA: radial artery; RGEA: right gastroepiploic artery; RIMA: right internal mammary artery; SVG: saphenous vein graft.

The seven 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 Fig. 2.

Pair-wise meta-analysis

A total of seven trials reported a direct comparison of RA versus SVG. Overall pair-wise meta-analysis found SVG associated with a non-significant trend towards an increased risk of functional graft occlusion (OR 1.47; 95% CI 0.69–3.15; Fig. 3) and complete graft occlusion (OR 1.64; 95% CI 0.77–3.49). A significant heterogeneity among studies was found for the primary outcome ($I^2 = 79\%$).

Table 1: Summary of studies included

First author (study acronym)	Year	Country	Study period	Sample size	RIMA	RA	SVG	RGEA	Type of randomization
Collins [10] (RVSP)	2008	UK	1998–2000	142	–	82	60	–	Inter-patients
Dreifaldt [11]	2013	Sweden	2004–2009	216	–	108	108	–	Within-patient randomization
Gaudino Study Group (AVGSRS) [12]	2005	Italy	1994–1997	60	20	20	20	–	Inter-patients
Gaudino Control Group (AVGSRS) [12]	2005	Italy	1994–1997	60	20	20	20	–	Inter-patients
Glineur [13]	2011	Belgium	2003–2006	238	–	–	116	122	Inter-patients
Goldman (VACSP) [14]	2011	US	2003–2009	733	–	366	367	–	Inter-patients
Hayward Group 1 (RAPCO) [15]	2011	Australia	1996–2004	365	179	186	0	–	Inter-patients
Hayward Group 2 (RAPCO) [15]	2011	Australia	1996–2004	214	–	104	110	–	Inter-patients
Deb (RAPS) [16]	2012	Canada	1996–2001	561	–	561	561	–	Within-patient randomization

RA: radial artery; RGEA: right gastroepiploic artery; RIMA: right internal mammary artery; SVG: saphenous vein graft.

Table 2: Grafted vessels, surgical techniques and angiographic follow-up details of studies included

First author (study acronym)	Territory grafted	Elective CABG (%)	On/off pump (%)	*n* patients with AnFU	*n* grafts with AnFU	Mean AnFU time
Collins (RVSP) [10]	Cx	100	On pump 100	103	59 RA vs 44 SVG	5 years
Dreifaldt [11]	Cx or RCA	100	On pump 100	99	99 RA vs 99 SVG	3 years
Gaudino Study Group (AVGSRS) [12]	Cx	100	On pump 100	60	20 RITA vs 20 RA vs 20 SVG	54 months
Gaudino Control Group (AVGSRS) [12]	Cx	100	On pump 100	60	20 RITA vs 20 RA vs 20 SVG	54 months
Glineur [13]	RCA	100	–	173	92 RGEA vs 81 SVG	3 years
Goldman (VACSP) [14]	Determined by surgeon	100	On pump 88	554	266 RA vs 296 SVG	1 year
Hayward Group 1 (RAPCO) [15]	Best vessel after LAD	RIMA 76–RA 77	On pump 100	227	105 RITA vs 122 RA	5.5 years
Hayward Group 2 (RAPCO) [15]	Best vessel after LAD	RA 71–SVG 81	On pump 100	110	51 RA vs 59 SVG	5.5 years
Deb (RAPS) [16]	Cx or RCA	65	–	234	234 RA vs 234 SVG	7.7 years

CABG: coronary artery bypass grafting; RA: radial artery; RGEA: right gastroepiploic artery; RIMA: right internal mammary artery; SVG: saphenous vein graft; AnFU: angiographic follow-up; LAD: left anterior descending artery; Cx: circumflex artery; RCA: right coronary artery.

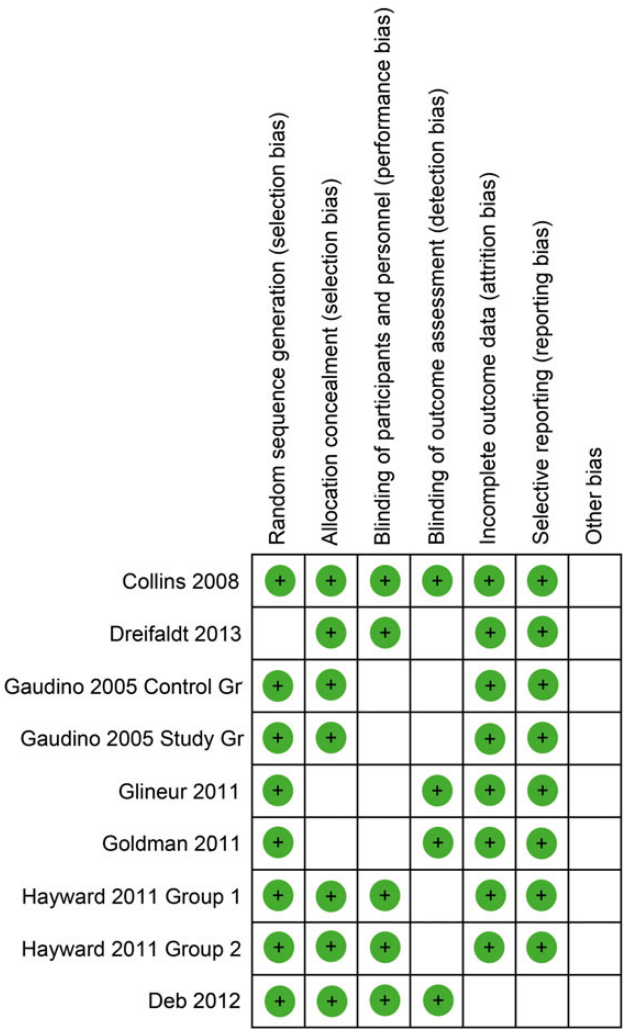

Figure 2: Risk of bias summary: review of authors' judgements about each risk of bias item for each included study.

Time to angiographic follow-up was identified as a significant source of variation (meta-regression $P < 0.001$, Fig. 4). When the analysis included trials with an angiographic follow-up of ≥4 years, no heterogeneity was found among studies ($I^2 = 18\%$) and SVG was significantly associated with a 2-fold increased risk of functional graft occlusion (OR 2.36; 95% CI 1.37–4.06) and complete graft occlusion (OR 2.64; 95% CI 1.60–4.35) when compared with the RA.

Another source of variation identified was the circumflex artery only as target vessel with a significant difference in effect estimates when the analysis was conducted pooling studies with the circumflex artery only as target vessel (OR 4.05; 95% CI 1.34–12.21; $P = 0.013$; $I^2 = 29\%$) or studies with both circumflex and right coronary arteries as the target vessel (OR 0.89; 95% CI 0.39–2.04; $P = 0.79$; $I^2 = 83\%$).

Leave-one-out meta-analysis suggested that effect estimates were not significantly driven from a single comparison (OR range 1.7–1.84; lower bound range 0.57–0.88; upper bound 2.4–4.5).

Only two trials by Gaudino *et al.* [12] reported a direct comparison of RIMA versus SVG after a mean follow-up time of 54 months. Pair-wise meta-analyses found SVG significantly associated with an increased risk of functional graft occlusion (OR 7.92; 95% CI 2.04–30.81) and SVG showed a non-significant trend towards a higher risk of complete graft occlusion (OR 3.86; 95% CI 0.73–20.48) when compared with the RIMA. No heterogeneity was found among the two studies ($I^2 = 0\%$).

A total of three trials reported a direct comparison of RIMA versus RA with a mean angiographic follow-up time of ≥4 years [12, 15]. Pair-wise meta-analyses showed that RIMA and RA were comparable in terms of risk of functional graft occlusion (OR 0.99; 95% CI 0.47–2.09), complete graft occlusion (OR 0.87; 95% CI 0.32–2.39) and string sign (OR 1.02; 95% CI 0.36–2.88). No heterogeneity was found among the two studies ($I^2 = 0\%$).

Network meta-analysis

Head-to-head relative effect estimates for functional and complete graft occlusion are summarized in Table 3. When the

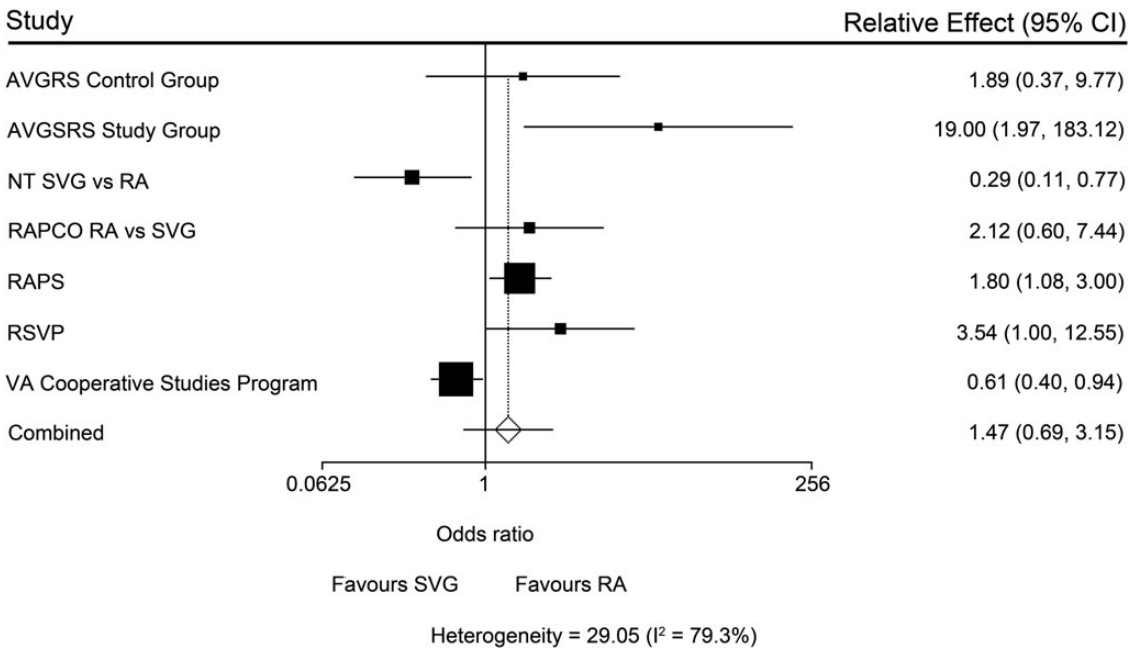

Figure 3: Pair-wise meta-analyses comparing radial artery (RA) versus saphenous vein graft (SVG) (outcome of interest: functional graft occlusion). 95% CI: 95% confidence interval; AVGRS: arterial versus venous bypass grafts in patients with in-stent restenosis study; NT: the no-touch saphenous vein as the preferred second conduit for coronary artery bypass grafting; RAPCO: radial artery patency and clinical outcomes trial; RAPS: radial artery patency study; RSVP: radial artery versus saphenous vein patency randomized trial; VA: veterans affairs.

network meta-analysis was conducted regardless of the mean time to angiographic follow-up, no conduit was found to have a significant superiority in terms of functional graft occlusion and complete graft occlusion. However, the RIMA was associated with a non-significant trend towards a decreased risk of functional and complete graft occlusion when compared with the RA, SVG and RGEA, thus achieving the highest probability to be the best conduit (75%) in a rank probability analysis (Fig. 5A). Moreover, RGEA was associated with a non-significant trend towards an increased risk of functional and complete graft occlusion when compared with the RIMA, RA and SVG. As a consequence, RGEA achieved the highest probability to be the worst conduit (82%). As only a 3-year RGEA angiographic follow-up was available, we repeated the analysis including only studies with an angiographic follow-up of ≤3 years, but RGEA was still found to have the highest probability to be the worst (71%).

No significant inconsistency was found for functional graft occlusion ($P = 0.13$), complete graft occlusion ($P = 0.28$) and string sign ($P = 0.09$).

When the analysis was restricted to trials with ≥4 years' angiographic follow-up time, SVG was significantly associated with a 4-fold and 3-fold increased risk of late (≥4 year) functional graft occlusion when compared with the RIMA and RA, respectively (Table 3). In addition, SVG was significantly associated with a 4-fold increased risk of late (≥4 year) complete graft occlusion when compared with the RA.

The RIMA was associated with a non-significant 27% absolute risk reduction for late (≥4 years) functional graft occlusion when compared with the RA. In a rank probability analysis (Fig. 5B), SVG achieved the highest probability to be the worst conduit (98%) and RIMA achieving the highest probability (74%) to be the best conduit.

No significant inconsistency was found for functional graft occlusion ($P = 0.19$) and complete graft occlusion ($P = 0.54$).

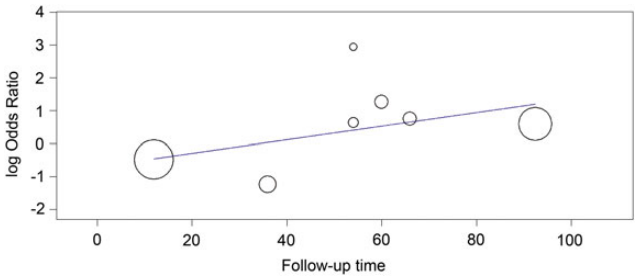

Figure 4: Meta-regression showing log odds ratio of studies comparing radial artery (RA) versus saphenous vein graft (SVG).

DISCUSSION

Cardiac surgeons should conduct each CABG operation with those patient factors and target-vessel considerations that predict optimum outcomes on the basis of all available evidence. The long-term patency of conduits used is one of the most important variables in determining long-term outcomes after CABG [1, 2].

Unfortunately, we do not have an unequivocal evidence basis for selecting bypass conduits beyond great confidence in the LITA-to-LAD coronary bypass graft [1]. Available RCTs have reported discordant results on the angiographic superiority of a second arterial conduit over the widely used SVG [10–16]. Similarly, there is a lack of an unequivocal evidence basis for selecting the best second arterial conduit [12, 15]. As a consequence multiple arterial grafting arterial still remains largely underutilized [7].

The present network meta-analysis, the first in the literature exploiting the totality of the evidence base, summarizes all the available evidence from RCTs comparing angiographic outcomes of second conduits including SVG, RIMA, RA and RGEA [10–16]. We found an angiographic superiority of RIMA and RA over SVG. The better patency rate from RIMA and RA over SVG was particularly evident when the angiographic follow-up was performed beyond 4 years from surgery.

Table 3: Relative effects from network meta-analyses including all RCTs (top) and RCTs with late (≥4 years, bottom) angiographic follow-up (not available for RGEA)

Relative effects for functional graft occlusion			
RA	5.71 (0.34–116.24)	0.54 (0.09–2.76)	1.77 (0.64–5.47)
	–	0.73 (0.19–2.50)	2.94 (1.36–9.00)
0.18 (0.01–2.94)	RGEA	0.09 (0.00–2.03)	0.30 (0.02–4.52)
		–	–
1.84 (0.36–10.58)	10.77 (0.49–314.59)	RIMA	3.30 (0.62–21.26)
1.36 (0.40–5.30)	–		4.07 (1.28–20.88)
0.56 (0.18–1.57)	3.31 (0.22–51.01)	0.30 (0.05–1.62)	SVG
0.34 (0.11–0.73)	–	0.25 (0.05–0.78)	
Relative effects for complete graft occlusion			
RA	5.74 (0.27–173.82)	0.96 (0.14–6.83)	2.31 (0.80–9.19)
	–	1.23 (0.25–5.75)	4.02 (1.67–16.00)
0.17 (0.01–3.70)	RGEA	0.17 (0.00–5.50)	0.41 (0.02–7.52)
–		–	–
1.04 (0.15–6.96)	5.83 (0.18–264.39)	RIMA	2.40 (0.36–20.63)
0.81 (0.17–4.01)	–		3.38 (0.78–22.20)
0.43 (0.11–1.25)	2.45 (0.13–47.90)	0.42 (0.05–2.79)	SVG
0.25 (0.06–0.60)	–	0.30 (0.05–1.28)	

RCT: randomized controlled trial; RA: radial artery; RGEA: right gastroepiploic artery; RIMA: right internal mammary artery; SVG: saphenous vein graft.

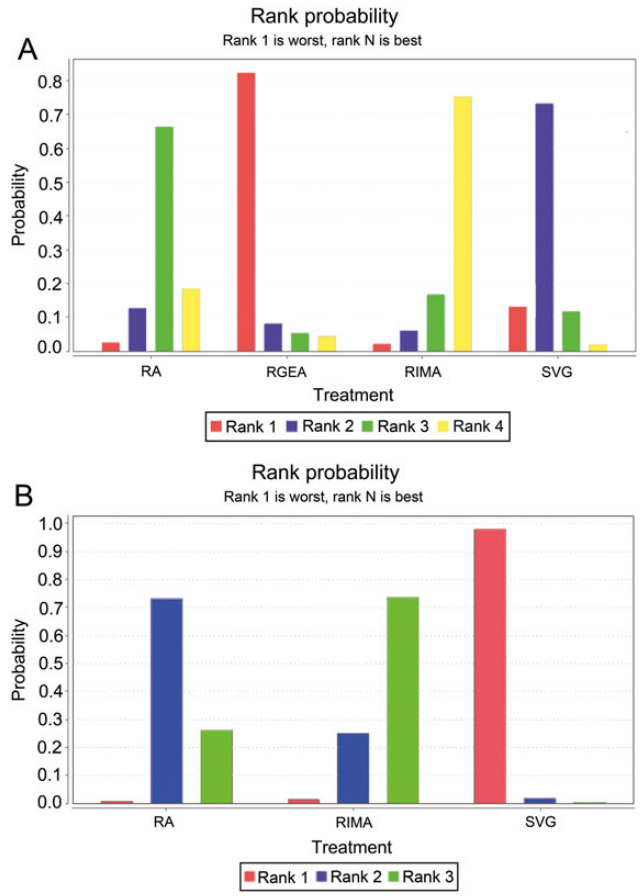

Figure 5: Rank probabilities for functional graft occlusion including all studies (**A**) and studies for late (≥4 years) angiographic follow-up only (**B**). RA: radial artery; RGEA: right gastroepiploic artery; RIMA: right internal mammary artery; SVG: saphenous vein graft.

The RIMA was associated with a non-significant 27% absolute risk reduction for late functional graft occlusion when compared with the RA, thus achieving the highest probability to be the best second conduit in CABG. At the same time, RA did not increase the risk for string sign when compared with RIMA and this result did not support the common perception of an increased risk of late vaso-reactivity associated with the RA [17].

Several large observational cohort studies have reported a long-term survival benefit in patients receiving RIMA or RA [2, 3]. The angiographic superiority of such arterial conduits demonstrated by the present meta-analysis represents the theoretical basis for the observed survival advantage from second arterial grafts instead of SVG and it strongly supports this association.

Of note, the present meta-analysis identified target vessel as source of heterogeneity in the comparison of RA versus SVG, suggesting a significant advantage from RA over SVG for circumflex artery targets only.

On the other hand, we found RGEA being the conduit associated with the highest risk of functional and complete graft occlusion, thus achieving the highest probability to be the worst conduit. This result supports previous reports showing RGEA associated with an increased risk of early failure especially when used as a composite free graft [18].

Drawbacks of meta-analyses, in general, are well known, and additional limitations of network meta-analyses can be envisioned [19]. 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, perioperative use of antispasmodic medications and postoperative anti-platelet therapy and anti-lipid therapy [20], which were not standardized among studies included.

Nonetheless, we emphasize that clinical decision-making is often based on incomplete evidence. Indeed, we remain positive that network meta-analyses based on indirect comparisons are exquisitely scientific, as they inform on what will be the outcomes of future randomized clinical trials.

In conclusion, the present network meta-analysis consistently demonstrated an angiographic superiority of RIMA and RA over SVG and hence, the recommendation for additional arterial conduits in patients undergoing CABG. By improving the long-term patency rate, this strategy is expected to improve late outcomes including survival as suggested by observational cohort studies [2, 3].

The present study strongly supports, on the basis of the trend towards a better patency rate observed for RIMA over RA, RIMA as the candidate to be the best second arterial conduit. However, the present analysis was not able to draw definitive conclusion on the angiographic superiority of RIMA over RA.

Taking into account that isolated elective CABG operative mortality nowadays is expected to be lower than 1% [21], the potential benefit from the RIMA over the RA should be well balanced by the risk of sternal wound complication with its high morbidity and mortality when bilateral IMA are used [22].

Until further evidence on the superiority of RIMA over RA is available, it seems reasonable to recommend the use of RIMA in patients at low risk of sternal wound complications. In addition, skeletonized technique should be considered to minimize the risk of sternal wound complication [23].

In the presence of concomitant risk factors for sternal wound infection such as diabetes on insulin and obesity [24], the RA should be considered instead of the RIMA to achieve multiple arterial grafting.

On the other hand, RGEA failed to show an angiographic superiority when compared with SVG, being associated with a higher risk of functional graft occlusion. In accordance with previous reports [18], the present network meta-analysis raises major concerns in supporting the use of RGEA as a first-choice second conduit in CABG.

Finally, since the superiority of arterial conduits including RIMA and RA over SVGs is consistently demonstrated, further randomized trials should be designed to clarify which is the best configuration when multiple arterial grafts are used and to identify which subgroup of patients are most likely to benefit from a second arterial conduit.

Conflict of interest: none declared.

REFERENCES

[1] Boylan MJ, Lytle BW, Loop FD, Taylor PC, Borsh JA, Goormastic M *et al.* Surgical treatment of isolated left anterior descending coronary stenosis. Comparison of left internal mammary artery and venous autograft at 18 to 20 years of follow-up. J Thorac Cardiovasc Surg 1994;107:657–62.

[2] Grau JB, Ferrari G, Mak AW, Shaw RE, Brizzio ME, Mindich BP *et al.* Propensity matched analysis of bilateral internal mammary artery versus single left internal mammary artery grafting at 17-year follow-up: validation of a contemporary surgical experience. Eur J Cardiothorac Surg 2012;41:770–5.

[3] Benedetto U, Codispoti M. Age cutoff for the loss of survival benefit from use of radial artery in coronary artery bypass grafting. J Thorac Cardiovasc Surg 2013;146:1078–84; discussion 1084–5.

[4] Glineur D, D'hoore W, Price J, Dorméus S, de Kerchove L, Dion R *et al*. Survival benefit of multiple arterial grafting in a 25-year single-institutional experience: the importance of the third arterial graft. Eur J Cardiothorac Surg 2012;42:284–90.
[5] Cao C, Manganas C, Horton M, Bannon P, Munkholm-Larsen S, Ang SC *et al*. Angiographic outcomes of radial artery versus saphenous vein in coronary artery bypass graft surgery: a meta-analysis of randomized controlled trials. J Thorac Cardiovasc Surg 2013;146:255–61.
[6] Benedetto U, Angeloni E, Refice S, Sinatra R. Radial artery versus saphenous vein graft patency: meta-analysis of randomized controlled trials. J Thorac Cardiovasc Surg 2010;139:229–31.
[7] Tatoulis J, Buxton BF, Fuller JA. The right internal thoracic artery: is it underutilized? Curr Opin Cardiol 2011;26:528–35.
[8] Song F, Harvey I, Lilford R. Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions. J Clin Epidemiol 2008;61:455–63.
[9] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement; PRISMA Group. BMJ 2009;339:b2535.
[10] Collins P, Webb CM, Chong CF, Moat NE. Radial artery versus saphenous vein patency randomized trial: five-year angiographic follow-up. Circulation 2008;117:2859–64.
[11] Dreifaldt M, Mannion JD, Bodin L, Olsson H, Zagozdzon L, Souza D. The no-touch saphenous vein as the preferred second conduit for coronary artery bypass grafting. Ann Thorac Surg 2013;96:105–11.
[12] Gaudino M, Cellini C, Pragliola C, Trani C, Burzotta F, Schiavoni G *et al*. Arterial versus venous bypass grafts in patients with in-stent restenosis. Circulation 2005;112:I265–9.
[13] Glineur D, D'hoore W, de Kerchove L, Noirhomme P, Price J, Hanet C *et al*. Angiographic predictors of 3-year patency of bypass grafts implanted on the right coronary artery system: a prospective randomized comparison of gastroepiploicartery, saphenous vein, and right internal thoracic artery grafts. J Thorac Cardiovasc Surg 2011;142:980–8.
[14] Goldman S, Sethi GK, Holman W, Thai H, McFalls E, Ward HB *et al*. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. JAMA 2011;305:167–74.
[15] Hayward PA, Buxton BF. The radial artery patency and clinical outcomes trial: design, intermediate term results and future direction. Heart Lung Circ 2011;20:187–92.
[16] 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.
[17] Khot UN, Friedman DT, Pettersson G, Smedira NG, Li J, Ellis SG. Radial artery bypass grafts have an increased occurrence of angiographically severe stenosis and occlusion compared with left internal mammary arteries and saphenous vein grafts. Circulation 2004;109:2086–91.
[18] Santos GG, Stolf NA, Moreira LF, Haddad VL, Simões RM, Carvalho SR *et al*. Randomized comparative study of radial artery and right gastroepiploic artery in composite arterial graft for CABG. Eur J Cardiothorac Surg 2002;21:1009–14.
[19] Song F, Xiong T, Parekh-Bhurke S, Loke YK, Sutton AJ, Eastwood AJ *et al*. Inconsistency between direct and indirect comparisons of competing interventions: meta-epidemiological study. BMJ 2011;343:4909.
[20] Bradshaw PJ, Jamrozik K, Gilfillan I, Thompson PL. Preventing recurrent events long term after coronary artery bypass graft: suboptimal use of medications in a population study. Am Heart J 2004;147:1047–53.
[21] Cavallaro P, Itagaki S, Seigerman M, Chikwe J. Operative mortality and stroke after on-pump vs off-pump surgery in high-risk patients: an analysis of 83 914 coronary bypass operations. Eur J Cardiothorac Surg. 2014;45: 159–64.
[22] Dai C, Lu Z, Zhu H, Xue S, Lian F. Bilateral internal mammary artery grafting and risk of sternal wound infection: evidence from observational studies. Ann Thorac Surg 2013;95:1938–45.
[23] Sá MP, Ferraz PE, Escobar RR, Vasconcelos FP, Ferraz AA, Braile DM *et al*. Skeletonized versus pedicled internal thoracic artery and risk of sternal wound infection after coronary bypass surgery: meta-analysis and meta-regression of 4817 patients. Interact CardioVasc Thorac Surg 2013;16:849–57.
[24] Crabtree TD, Codd JE, Fraser VJ, Bailey MS, Olsen MA, Damiano RJ Jr. Multivariate analysis of risk factors for deep and superficial sternal infection after coronary artery bypass grafting at a tertiary care medical center. Semin Thorac Cardiovasc Surg 2004;16:53–61.

APPENDIX. CONFERENCE DISCUSSION

Dr M. Sousa Uva *(Lisbon, Portugal)*: You and your co-authors have conducted a very elegant and well performed study on an important topic. You tried to answer two questions: to establish, first, whether there is evidence supporting an angiographic superiority of arterial conduits over saphenous vein grafts, and, second, to compare arterial conduits and establish which arterial grafts were the second best after the left internal thoracic artery.

You have used a very accurate search strategy to look for randomized trials comparing graft patency after four years, and you identified nine trials, six of which included a follow-up angio at equal to or greater than four years. The results showed, in summary, that saphenous vein grafts are significantly associated with a four-fold and a three-fold increased risk for late functional graft occlusion when compared with right internal mammary artery and radial artery, respectively, and that the right internal mammary artery was associated with a non-significant, 27%, absolute risk reduction for functional graft occlusion when compared with the radial artery.

I have some considerations regarding the meaning for us surgeons of what a network meta-analysis is, and this may be something mysterious to some of us. So just to summarize, I think the advantage of a network meta-analysis over a standard pairwise meta-analysis is that it facilitates indirect comparisons of multiple interventions that have not been studied in a head-to-head fashion. It has the advantage, also, that it allows these indirect comparisons, and so more data is incorporated and a bigger picture is therefore obtained. However, we should clearly state that there are a certain number of limitations and let me just remind you of them.

First, evidence that is procured by small trials tends to be susceptible to greater bias, and we have here one trial by Gaudino of only 60 patients, for example. Inferences may be driven largely from evidence of one or a few treatments in comparison. Bias can arise from variation in the distribution of treatment effect modifiers between comparisons, for example, in study characteristics or the distribution of patient characteristics across trials, if these characteristics between trials are treatment modifiers, meaning that they have an influence on the treatment effect. In this case there are different treatment effects across trials and these can result in bias. Finally, the ranking of treatments may change drastically just when a new trial is introduced and so those ranking probabilities can be fragile. So we should place more emphasis on the treatment effects rather than this ranking of probabilities.

However, studies like this one can help us see what the gaps are in evidence and orient further investigations towards the need for additional multicentre large trials comparing the right internal mammary artery with best harvested saphenous veins as well as radial arteries. You know that many factors affect patency, namely, the method of conduit harvesting is extremely important, graft quality, graft preservation, and geometrical arrangement, as we have just seen this morning. So the conduit choice should clearly be individualized for each patient.

I have two questions. First, knowing that patient level data can improve parameter estimation of network meta-analysis models, did you have patient level data available in any of the randomized trials?

Dr Benedetto: In the present analysis we did not investigate the effect of covariates among studies. We conducted an inconsistency check. We did not find significant inconsistency among studies, meaning that conduit outcomes were not significantly influenced by study and patient level data, thus making our conclusions stronger. But I completely agree with you that there are a lot of variables that can affect this comparison.

Dr Sousa Uva: You answered my second question actually already. The question was whether you looked in the individual patient level data in each or not?

Dr Benedetto: I didn't.

Dr Sousa Uva: Finally, what do you suggest the next step would be to improve the degree of certainty in our daily practice to inform our choice for the second graft?

Dr Benedetto: The superiority of arterial grafts over saphenous vein grafts is strongly supported by the available evidence. However, the best graft configuration for the second arterial conduit remains unknown. In addition, which patients need a right mammary artery rather than a radial artery is also unknown. Therefore, I think we should spend further resources to compare arterial grafts in different configurations and clinical settings, instead of continuing to compare arterial grafts versus saphenous vein grafts.

Dr T. Schwann *(Toledo, OH, USA)*: Although we may quibble as to what may be the second best arterial graft, I think what is obvious here is what is the worst graft possible, and I think the conclusion is unanimous that we should be using arterial grafts rather than vein grafts.