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**ORIGINAL ARTICLE**



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# Radial artery versus saphenous vein versus right internal thoracic artery for coronary artery bypass grafting

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**Key question**

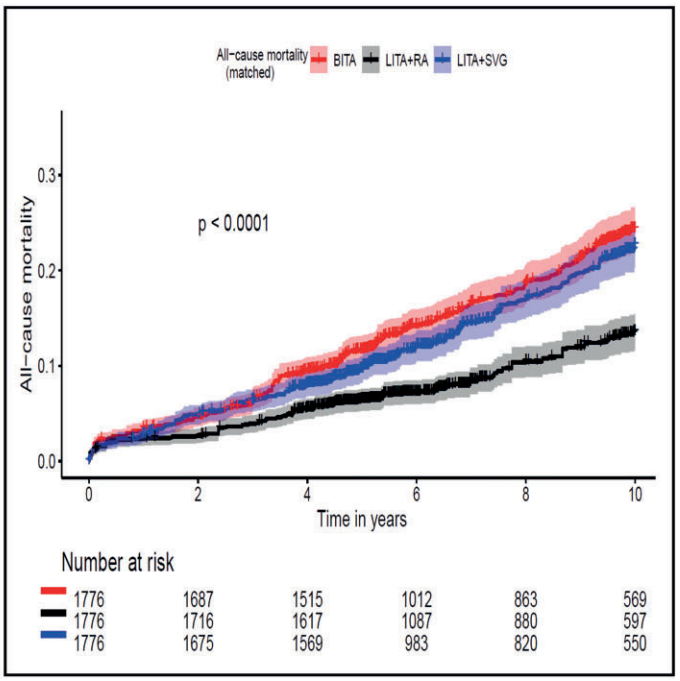
Radial artery, right internal thoracic artery, and saphenous vein: what is the best second conduit for coronary surgery?

**Key finding(s)**

Mortality and adverse events were lower in the radial artery group vs right internal thoracic artery and saphenous vein.

**Take-home message**

In coronary surgery patients, the radial artery provides better clinical outcomes vs right internal thoracic artery and saphenous vein.



## Abstract

**OBJECTIVES:** We used individual patient data from 4 of the largest contemporary coronary bypass surgery trials to evaluate differences in long-term outcomes when radial artery (RA), right internal thoracic artery (RITA) or saphenous vein graft (SVG) are used to complement the left internal thoracic artery-to-left anterior descending graft.

**METHODS:** Primary outcome was all-cause mortality. Secondary outcome was a composite of major adverse cardiac and cerebrovascular events (all-cause mortality, myocardial infarction and stroke). Propensity score matching and Cox regression were used to reduce the effect of treatment selection bias and confounders.

**RESULTS:** A total of 10 256 patients (1510 RITA; 1385 RA; 7361 SVG) were included. The matched population consisted of 1776 propensity score-matched triplets. The mean follow-up was 7.9 ± 0.1, 7.8 ± 0.1 and 7.8 ± 0.1 years in the RITA, RA and SVG cohorts respectively. All-cause mortality was significantly lower in the RA versus the SVG [hazard ratio (HR) 0.62, 95% confidence interval (CI): 0.51–0.76, $P = 0.003$] and the RITA group (HR 0.59, 95% CI 0.48–0.71, $P = 0.001$). Major adverse cardiac and cerebrovascular event rate was also lower in the RA group versus the SVG (HR 0.78, 95% CI 0.67–0.90, $P = 0.04$) and the RITA group (HR 0.75, 95% CI 0.65–0.86, $P = 0.02$). Results were consistent in the Cox-adjusted analysis and solid to hidden confounders.

**CONCLUSIONS:** In this pooled analysis of 4 large coronary bypass surgery trials, the use of the RA was associated with better clinical outcomes when compared to SVG and RITA.

**Keywords:** Coronary artery bypass grafting • Multiple arterial grafting • Radial artery

**ABBREVIATIONS**

| | |
|---|---|
| BITA | Bilateral internal thoracic artery |
| CABG | Coronary artery bypass grafting |
| CI | Confidence interval |
| HR | Hazard ratio |
| LITA | Left internal thoracic artery |
| MACCE | Major adverse cardiac and cerebrovascular events |
| MAG | Multiple arterial grafting |
| MI | Myocardial infarction |
| PS | Propensity score |
| RA | Radial artery |
| RCTs | Randomized controlled trials |
| RITA | Right internal thoracic artery |
| SITA | Single internal thoracic artery |
| SVG | Saphenous vein graft |

## INTRODUCTION

Observational studies have reported an association between the use of multiple arterial grafting (MAG) for coronary artery bypass grafting (CABG) and improved long-term outcomes compared to the use of a single arterial grafting, although this has not been confirmed in randomized trials [1].

In current surgical practice, MAG is generally achieved by adding either the radial artery (RA) or the right internal thoracic artery (RITA) to the gold-standard left internal thoracic artery (LITA) to left anterior descending anastomosis. The RA and the RITA have different histologic and surgical characteristics and it is conceivable that differences in outcome between the 2 arterial conduits may exist. This, however, has not been extensively investigated to date and the available evidence is mixed [2].

We have used a merged database containing individual patient data from some of the largest contemporary CABG trials to evaluate differences in long-term outcomes when the RA, the RITA or the saphenous vein graft (SVG) are used to complement the LITA to left anterior descending graft.

## MATERIALS AND METHODS

### Ethics statement

Ethics approval and participant consent were obtained locally by each study team. Weill Cornell Medicine Institutional Review Board waived the need for ethics approval for the pooled analysis. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Methods

The rationale for the current analysis, analytic strategies and prespecified end points were generated during the performance of a previous individual patient data pooled analysis including CABG randomized controlled trials (RCTs) [3]. Details of the search strategy and of the methods used for data pooling have been published previously [4]. For the purpose of the present analysis, the largest contemporary RCTs where CABG patients received bilateral internal thoracic artery (BITA), LITA + RA or LITA + SVG were identified and necessary patient-level data were obtained from each trials team. Patients were stratified based on the second graft received at surgery and the longest available follow-up was used.

### Data collection and merging

After identification of eligible trials, the individual trial teams were contacted to obtain the necessary patient-level data and they all agreed. Detailed specifications of core minimum de-identified data requirements were provided to each trial team. De-identified data were received by the coordinating centre at Weill Cornell Medicine and checked for quality, completion and consistency with previous publications. Data were checked for missing values, intra-field data integrity and inter-field inconsistencies both within each RCT and across the RCTs. Discrepancies were resolved through direct consultation with the individual trials' teams. Data elements were then consolidated into a final database.

## Outcomes

The primary outcome was all-cause mortality. The secondary outcome was a composite of major adverse cardiac and cerebrovascular events (MACCE) including all-cause mortality, any myocardial infarction (MI) and any stroke. Additional analyses for the individual non-fatal components of the secondary outcome and for repeat revascularization were also performed. For all events, individual trial definitions were used (details are in Supplementary Material, Table S1).

## Statistical analysis

Categorical variables are presented as frequencies and percentages and continuous variables as means and standard deviations or medians and interquartile ranges based on normality.

To reduce the effect of treatment selection bias and potential confounders we used different adjustment strategies. In the main analysis, we adjusted for the following variables using propensity score (PS) matching with replacement: age, sex, New York Heart Association grade III or IV, creatinine (μmol/l), previous MI, previous percutaneous transluminal coronary angioplasty, hypertension, diabetes mellitus, renal insufficiency (as defined by each trial), previous stroke, peripheral vascular disease, left ventricular ejection fraction <50%, off-pump CABG, number of grafts used and trial identifier. To generate comparable matched triplets, the following method was used: considering 2 treatments, $Tr_{1\ (BITA)}$ and $Tr_{2\ (LITA+RA)}$, and a control, C (LITA + SVG), we estimated PS with 3 separate logistic regression models where model 1 predicts $Tr_1$ with C, model 2 predicts $Tr_2$ with C and model 3 predicts $Tr_1$ with $Tr_2$ [5]. Since each unit has a PS in 2 of the 3 models, their scores were connected. We then calculated 3 distances between PS for each possible matched triplet using the 3 models. Given those distances, the matched triplets with the smallest standardized distance (i.e. $D_{x,y} = |PS_x - PS_y|$) were retained. Distances greater than the calliper, 0.25 standard deviations of the logit of the PS, were eliminated as recommended by Rosenbaum and Rubin [6]. For this analysis, TriMatch R algorithm was used [7]. Balance between groups was assessed using standardized mean difference. A value of higher than 0.20 was considered as an indication of residual imbalance. Kaplan–Meier and stratified log rank methods and univariate Cox regression were used to compare time to event outcomes among matched groups. Treatment effect was estimated using matching weights to account for matching with replacement. Standard errors were calculated using clustered robust standard errors which account for both the matching weights and pair membership.

Analyses of non-fatal time-to-event outcomes was performed by applying the Fine–Gray competing risk framework to account for the competing risk of death [8].

In a sensitivity analysis, the association of BITA and LITA + RA with the primary and secondary outcome was tested using multivariable mixed Cox regression model with trial identifier as a random effect to account for clustering; covariates included in the Cox model were the same used in the PS model. For this analysis, *E*-values were calculated to assess the solidity of the results to unaccounted confounders.

All *P*-values were two-sided, with $P < 0.05$ considered to indicate statistical significance. No adjustment for multiplicity was used as this is a *post hoc* analysis and results must be seen as hypothesis generating. All statistical analyses were performed with R Statistical Software (version 4.0.5; R Foundation for Statistical Computing, Vienna, Austria).

# RESULTS

## Trials and patients included in the analysis

Four trials are included in this pooled analysis. A brief description of each trial is provided below.

In the *Arterial Revascularization Trial (ART trial)* [9], 3102 CABG patients were randomly assigned to bilateral or single internal thoracic artery (SITA) grafting (1548 vs 1554 patients, respectively). Patients were enrolled from 2004 to 2007 at 28 hospitals from 4 continents and a total of 7 countries. At 10-year follow-up, the authors found no significant between-group difference in the rate of death from any cause [hazard ratio (HR) 0.96, 95% confidence interval (CI) 0.82–1.12] and in the composite outcome of death, MI or stroke (HR 0.90, 95% CI 0.79–1.03).

In the *CABG Off or On Pump Revascularization Study (CORONARY)* [10], 4752 patients were randomly assigned to undergo off-pump or on-pump CABG (2375 vs 2377 patients, respectively). Patients were enrolled from 2006 to 2011 at 79 centres from 4 continents and a total of 19 countries. At 4.8-year follow-up, the rate of the composite outcome of death, MI, stroke, renal failure or repeat revascularization was similar between the 2 groups (HR 0.98, 95% CI 0.87–1.10).

In the *Project of Ex-Vivo Vein Graft Engineering via Transfection IV trial (PREVENT IV)* [11], 3014 patients undergoing primary CABG with at least 2 planned SVGs were randomly assigned to undergo *ex vivo* vein grafts treatment with either edifoligide or placebo (1508 vs 1506 patients, respectively). Patients were enrolled from 2002 to 2003 at 107 sites in the Unites States. At 1-year, edifoligide had no effect on the primary end point of SVG failure (45.2% in the edifoligide group vs 46.3% in the placebo group; odds ratio 0.96, 95% CI 0.80–1.14, $P = 0.66$), on any secondary angiographic end point or on the incidence of major adverse cardiac events (6.7% vs 8.1%; HR 0.83, 95% CI 0.64–1.08, $P = 0.16$). At 5-year follow-up, patients randomized to edifoligide and placebo had similar rates of death (11.7% vs 10.7%), MI (2.3% vs 3.2%), revascularization (14.1% vs 13.9%) and rehospitalization (61.6% vs 62.5%). The 5-year composite outcome of death, MI or revascularization occurred at similar frequency in patients assigned to edifoligide and placebo (26.3% vs 25.5%; HR 1.03, 95% CI 0.89–1.18, $P = 0.721$).

In the *Radial Artery Patency and Clinical Outcomes (RAPCO) trial* [12], 2 groups were tested: in a younger group (group 1: $n = 394$, <70 years [<60 years if diabetic]), LITA + RA was compared with BITA; in an older group (group 2: $n = 225$, ≥70 years [≥60 years if diabetic]), LITA + RA was compared with LITA + SVG. Patients were enrolled from 1996 to 2005 at a single centre in Australia. In the LITA + RA versus BITA comparison, the 10-year patency was 89% for LITA + RA vs 80% for BITA (HR for graft failure 0.45, 95% CI 0.23–0.88) and 10-year patient survival was 90.9% in the LITA + RA arm vs 83.7% in the BITA arm (HR for mortality 0.53, 95% CI 0.30–0.95). In the LITA + RA versus LITA + SVG comparison, the 10-year patency was 85% for the LITA + RA vs 71% for the LITA + SVG (HR for graft failure 0.40, 95% CI 0.15–1.00) and 10-year patient survival was 72.6% for the LITA + RA group vs 65.2% for the LITA + SVG group (HR 0.76, 95% CI 0.47–1.22).

Overall, 10 256 patients were included in the pooled analysis (1510 BITA; 1385 LITA + RA; 7361 LITA + SVG). Details of the

**Table 1:** Baseline and operative patients' characteristics of the 1776 propensity score-matched triplets

| | BITA | LITA + RA | LITA + SVG | SMD |
|---|---|---|---|---|
| Age, median [IQR] | 64.0 [58.2, 70.4] | 62.8 [57.1, 69.0] | 64.1 [58.5, 70.0] | 0.09 |
| Females, *n* (%) | 261 (14.7) | 216 (12.2) | 214 (12.0) | 0.05 |
| Renal insufficiency, n (%) | 14 (0.8) | 5 (0.3) | 5 (0.3) | 0.05 |
| Diabetes, *n* (%) | 527 (29.7) | 532 (30.0) | 596 (33.6) | 0.06 |
| Previous MI, *n* (%) | 703 (39.6) | 683 (38.5) | 667 (37.6) | 0.03 |
| LVEF <50%, *n* (%) | 813 (45.8) | 747 (42.1) | 780 (43.9) | 0.05 |
| Creatinine (μmol/l), median [IQR] | 88.4 [79.5, 106.0] | 88.4 [78.0, 102.0] | 89.0 [79.6, 102.0] | 0.07 |
| NYHA III–IV, *n* (%) | 428 (24.1) | 371 (20.9) | 389 (21.9) | 0.05 |
| Hypertension, *n* (%) | 1315 (74.0) | 1326 (74.7) | 1278 (72.0) | 0.04 |
| PVD, n (%) | 158 (8.9) | 137 (7.7) | 135 (7.6) | 0.03 |
| Previous stroke, n (%) | 89 (5.0) | 69 (3.9) | 63 (3.5) | 0.05 |
| Previous PCI, n (%) | 260 (14.6) | 277 (15.6) | 236 (13.3) | 0.04 |
| Off pump surgery, n (%) | 780 (43.9) | 688 (38.7) | 697 (39.2) | 0.07 |
| Number of grafts, median [IQR] | 3.0 [3.0, 4.0] | 3.0 [3.0, 4.0] | 3.0 [3.0, 4.0] | 0.12 |
| Trials[a] | | | | 0.07 |
| ART | 1063 (59.9) | 1020 (57.4) | 1026 (57.8) | |
| CORONARY | 505 (28.4) | 584 (32.9) | 567 (31.9) | |
| PREVENT-IV | 208 (11.7) | 172 (9.7) | 183 (10.3) | |

[a]RAPCO was excluded from the matched analysis due to missing variables.

BITA: bilateral internal thoracic artery; IQR: interquartile range; LITA: left internal thoracic artery; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; RA: radial artery; SMD: standardized mean difference; SVG: saphenous vein graft.

**Table 2:** Event rates for primary and secondary outcomes, for the individual components of the secondary outcome and for repeat revascularization in the matched cohort

| | | | |
|---|---|---|---|
| **All-cause mortality** | | | |
| | **No. events** | **Survival probability** | **95% CI** |
| BITA | 340 | 0.77 | 0.74–0.80 |
| LITA + RA | 184 | 0.86 | 0.82–0.90 |
| LITA + SVG | 301 | 0.78 | 0.74–0.82 |
| **MACCE** | | | |
| | **No. of events** | **Survival probability** | **95% CI** |
| BITA | 551 | 0.64 | 0.61–0.68 |
| LITA + RA | 411 | 0.71 | 0.66–0.77 |
| LITA + SVG | 506 | 0.66 | 0.61–0.70 |
| **Myocardial infarction** | | | |
| | **No. events** | **Cumulative incidence** | **95% CI** |
| BITA | 120 | 0.08 | 0.05–0.10 |
| LITA + RA | 121 | 0.08 | 0.05–0.12 |
| LITA + SVG | 103 | 0.06 | 0.05–0.07 |
| **Stroke** | | | |
| | **No. events** | **Cumulative incidence** | **95% CI** |
| BITA | 52 | 0.04 | 0.02–0.05 |
| LITA + RA | 37 | 0.03 | 0.01–0.05 |
| LITA + SVG | 64 | 0.05 | 0.03–0.07 |
| **Repeat revascularization** | | | |
| | **No. events** | **Cumulative incidence** | **95% CI** |
| BITA | 152 | 0.12 | 0.09–0.14 |
| LITA + RA | 148 | 0.11 | 0.07–0.15 |
| LITA + SVG | 162 | 0.12 | 0.08–0.16 |

BITA: bilateral internal thoracic artery; CI: confidence interval; LITA: left internal thoracic artery; MACCE: major adverse cardiac and cerebrovascular events; RA: radial artery; SVG: saphenous vein graft.

overall patients' population are provided in Supplementary Material, Table S2; details of the contribution of each included trial to the unmatched and matched cohorts and of conduits from each trial are provided in Supplementary Material, Table S3.

The matched population consisted of 1776 PS-matched triplets among which good balance was achieved (Supplementary Material, Figs. S1 and S2). Baseline and operative characteristics of the matched cohorts are reported in Table 1. The mean follow-up time was 7.9 ± 0.1, 7.8 ± 0.1 and 7.8 ± 0.1 years in the BITA, LITA + RA and LITA + SVG cohorts, respectively.

## Primary outcome: all-cause mortality

All-cause mortality rates were 14.3% in the LITA + RA group, 22.1% in the LITA + SVG group and 22.6% in the BITA group (Table 2). The risk of all-cause mortality was significantly lower in the LITA + RA group when compared to the LITA + SVG group (HR 0.62, 95% CI 0.51–0.76, $P = 0.003$) and the BITA group (HR 0.59, 95% CI 0.48–0.71, $P = 0.001$) (Fig. 1, Central Image and Tables 2 and 3). No difference in all-cause mortality risk was found when BITA was compared to LITA + SVG (HR 1.07, 95% CI 0.90–1.27, $P = 0.62$).

The results using Cox regression were consistent with the results of the analysis using PS matching: the use of LITA + RA was significantly and inversely associated with the incidence of all-cause mortality (HR 0.76, 95% CI 0.63–0.92, $P = 0.004$,), whereas there was no significant association between the use of BITA and the incidence of all-cause mortality (HR 1.02, 95% CI 0.88–1.19, $P = 0.75$, see also Supplementary Material, Table S4). The *E*-value calculation for the LITA + RA inverse association with mortality showed good solidity of the association to unmeasured confounders (*E*-value = 1.97).

## Secondary outcome: major adverse cardiac and cerebrovascular events

In the matched cohort, MACCE rates were 29.1% in the LITA + RA group, 34.3% in the LITA + SVG group and 35.7% in the BITA group (Table 2). The risk of MACCE was significantly lower in the

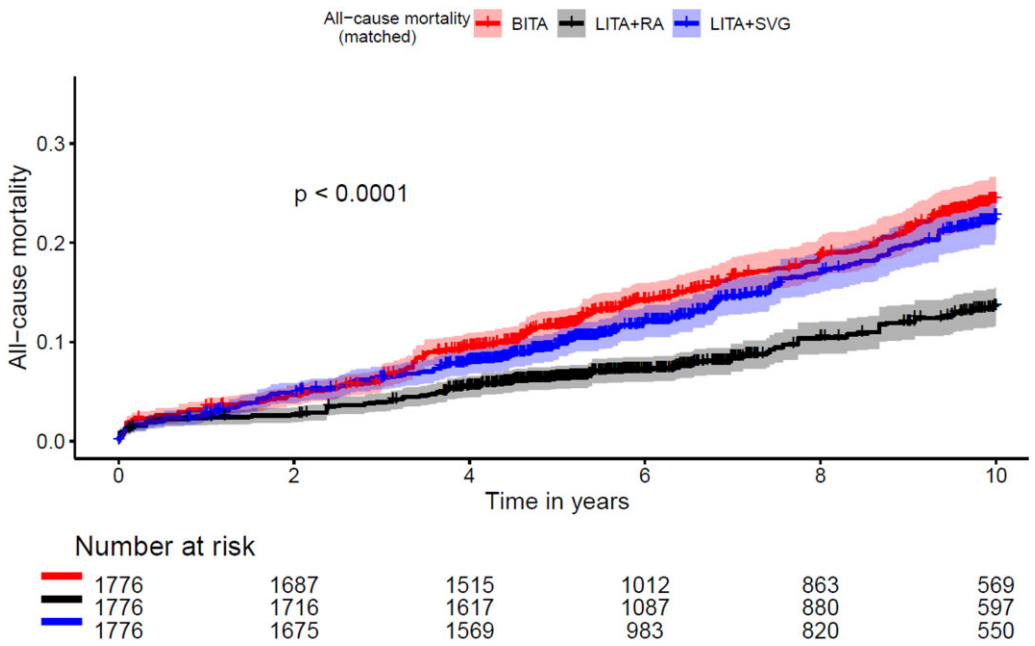



**Figure 1:** Kaplan–Meier curves for all-cause mortality in the matched cohorts (hazard ratio for left internal thoracic artery + radial artery versus left internal thoracic artery + saphenous vein graft: 0.62, 95% CI: 0.51–0.76, $P = 0.003$; hazard ratio for left internal thoracic artery + radial artery versus bilateral internal thoracic artery: 0.59, 95% confidence interval 0.48–0.71, $P = 0.001$). BITA: bilateral internal thoracic artery; CI: confidence interval; HR: hazard ratio; LITA: left internal thoracic artery; RA: radial artery; SVG: saphenous vein graft.

**Table 3:** Main results for the primary and secondary outcomes in the matched cohort

| | **All-cause mortality** | |
|---|---|---|
| | **Hazard ratio (95% CI)** | ***P*-Value** |
| LITA + SVG | Reference | |
| BITA | 1.07 (0.90–1.27) | 0.62 |
| LITA + RA | 0.62 (0.51–0.76) | 0.003 |
| BITA | Reference | |
| LITA + RA | 0.59 (0.48–0.71) | 0.001 |
| LITA + SVG | 0.94 (0.79–1.12) | 0.59 |
| | **MACCE** | |
| | **Hazard ratio (95% CI)** | ***P*-Value** |
| LITA + SVG | Reference | |
| BITA | 1.04 (0.91–1.19) | 0.66 |
| LITA + RA | 0.78 (0.67–0.90) | 0.04 |
| BITA | Reference | |
| LITA + RA | 0.75 (0.65–0.86) | 0.02 |
| LITA + SVG | 0.96 (0.84–1.10) | 0.66 |

BITA: bilateral internal thoracic artery; CI: confidence interval; LITA: left internal thoracic artery; MACCE: major adverse cardiac and cerebrovascular events; RA: radial artery; SVG: saphenous vein graft.

LITA + RA group when compared to the LITA + SVG group (HR 0.78, 95% CI 0.67–0.90, $P = 0.04$) and the BITA group (HR 0.75, 95% CI 0.65–0.86, $P = 0.02$) (Fig. 2 and Tables 2 and 3). No difference in the risk of MACCE was found when BITA was compared to LITA + SVG (HR 1.04, 95% CI 0.91–1.19, $P = 0.66$).

At Cox regression, the use of LITA + RA, but not of BITA, was significantly and inversely associated with the incidence of MACCE (HR 0.77, 95% CI 0.67–0.88, $P < 0.001$ for the RA and HR 1.00, 95% CI 0.89–1.13, $P = 1.00$ for the BITA—see also Supplementary Material, Table S4). Again, the *E*-value calculation for the LITA + RA inverse association with MACCE showed good solidity of the association to unmeasured confounders (*E*-value = 1.94).

The individual event rates for MI, stroke and repeat revascularization in the matched population are provided in Table 2 and Supplementary Material, Fig. S3.

Results in the unmatched cohort are provided in Supplementary Material, Figs. S4 and S5 and Supplementary Material, Tables S5 and S6.

## DISCUSSION

In this pooled analysis of 10 256 CABG patients followed up for 7 years, the rates of all-cause mortality and MACCE were significantly lower in the LITA + RA group when compared to the LITA + SVG group and to the BITA group.

The available evidence on the effect of MAG for CABG is mixed. Observational studies generally support an association between MAG (using either RA or RITA) and improved long-term outcomes. In a meta-analysis of 29 observational studies (89 399 patients), those who received BITA had significantly improved long-term survival and cardiovascular events compared to patients who received an SITA [13]. Similarly, in a meta-analysis of 14 adjusted observational studies (20 931 patients), the use of RA, rather than SVG to complement the LITA, was associated with significantly better survival at 6.6 years of follow-up [14].

However, in the ART trial, among 3102 patients randomized to receive SITA or BITA, there was no significant difference in survival and event-free survival at 10-year follow-up [9]. On the other hand, in a pooled analysis of individual patients data from 5 randomized trials, the use of RA as the second conduit was associated with a significant reduction in the risk of cardiac events and a survival benefit at 10 years compared to the use of SVG [15].

Randomized trials have shown that the RA has better mid-and long-term patency rate than the SVG, and this may be the

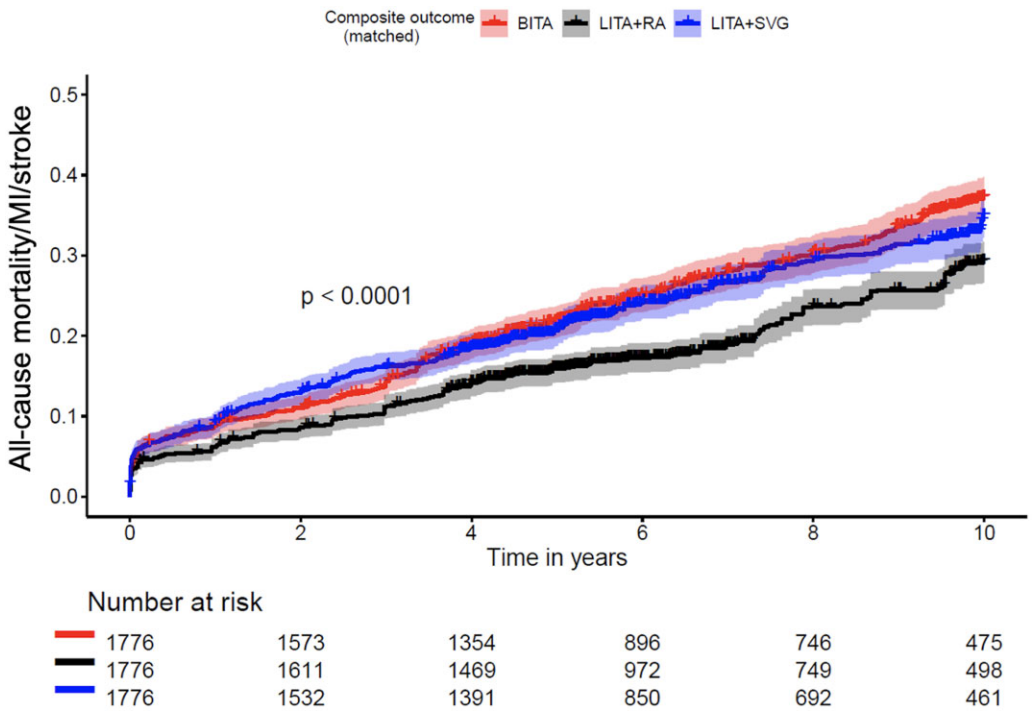



**Figure 2:** Kaplan–Meier curves for the composite outcome of major adverse cardiac and cerebrovascular events in the matched cohorts (hazard ratio for left internal thoracic artery + radial artery versus left internal thoracic artery + saphenous vein graft: 0.78, 95% confidence interval 0.67–0.90, $P = 0.04$; hazard ratio for left internal thoracic artery + radial artery versus bilateral internal thoracic artery: 0.75, 95% confidence interval 0.65–0.86, $P = 0.02$). BITA: bilateral internal thoracic artery; CI: confidence interval; HR: hazard ratio; LITA: left internal thoracic artery; MI: myocardial infarction; RA: radial artery; SVG: saphenous vein graft.

mechanistic explanation of the improved outcomes described with this arterial conduit; the evidence is less strong for the comparison between RITA and SVG. In a network meta-analysis of 14 randomized trials (3651 grafts) the RA, but not the RITA, had significantly better patency rate at 5-year follow-up when compared to SVG [16].

The only randomized trial that has directly compared the RA and the RITA is the RAPCO trial where at 10-year follow-up the RA had significantly better patency rate and survival (with the caveat that both conduits were used proximally anastomosed to the aorta which may have penalized the smaller and more fragile RITA). In 2 previous meta-analyses of observational data, we have reported conflicting results for the RA versus RITA comparison, but this may be due to small study effect and imperfect adjustment when pooling aggregate rather than individual data [17, 18].

Of note in the ART trial, while the BITA versus LITA comparison was neutral, a *post hoc* analysis based on the number of arterial graft received (including the RA) found that patients who received MAG had better 10-year survival and event-free survival [9]. This is likely explained by the survival benefit seen in ART patients who received an RA graft [19] and is consistent with our findings.

The RA and RITA have different biologic properties and, most importantly, surgical characteristics. Due to the muscular nature of its wall, the RA is potentially more prone to vasospasm; such concerns, however, have been greatly reduced after the demonstration of progressive morphofunctional remodelling of the artery towards an elastomuscular profile after implantation in the coronary circulation [20, 21]. The internal thoracic arteries have a discontinuous internal elastic lamina and a relatively thin media with multiple elastic laminae, without a significant muscular component, explaining their reduced tendency for spasm and the development of atherosclerosis [21, 22]. Because of these histologic differences as well as the larger diameter and superior length, the RA is technically easier to use while the RITA is more fragile and often requires complex technical solutions to reach distal or multiple targets [2]. The surgeon's volume-to-outcome association has been shown to be stronger for the RITA than for the RA [23, 24] and the use of RITA by less-experienced surgeons has been associated with a marginal increase in operative mortality [25].

It seems likely, although unproven to date, that the reason for the reported differences between the 2 arterial conduits is technical rather than biological. Recent concerns about a possible effect of the RITA harvesting technique on patency and outcome may also have played a role [26]; unfortunately, the pooled trials did not consistently capture the harvesting technique, and this could not be tested in our analysis.

## Limitations

This study has limitations. Outcome definitions and event adjudication were not standardized in the included trials, although all used an independent adjudication committee. However, we used all-cause mortality as the primary outcome to minimize differences due to heterogeneity in event definitions between trials. It is likely that there was heterogeneity in surgical techniques and postoperative protocols between the included trials and the individual participating sites. Also, different trials contributed differently to the 3 study groups. However, we adjusted for clustering using different techniques in all our models. Importantly, the comparisons we have presented are not randomized and, even after extensive statistical adjustment, there may be biases and residual imbalance that could influence our findings. Moreover, we

were not able to include graft configuration in the PS analysis. On the other hand, it is reassuring that the results were consistent using different adjustment methods and that the *E*-value calculations showed that only unmeasured confounders with moderate-to-high association with the treatment and the outcome would explain the reported results.

However, as we have noted elsewhere [27], comparative observational analyses in surgery suffer from treatment allocation and experience bias (with 'healthier' patients generally receiving the more complex operation or the one perceived as having better long-term results and more experienced surgeons performing more often the more complex procedures), so the reported results need to be tested in an adequately powered RCT.

## CONCLUSION

In conclusion, in this pooled analysis of 4 large CABG trials, we generate the important hypothesis that the use of LITA + RA is associated with better clinical outcomes when compared to LITA + SVG and BITA. Further randomized studies assessing long-term outcomes after CABG with LITA + RA versus BITA or LITA + SVG are needed.

## SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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None.

**Conflict of interest:** Dr Di Franco has consulted for Servier and served as Advisory Board Member for Scharper. All other authors declare no conflicts of interest.

## Data availability

Data collected for the study will be made available by the corresponding author upon reasonable request after publication.

## Author contributions

**Mario Gaudino:** Conceptualization; Investigation; Methodology; Project administration; Supervision; Validation; Writing—original draft; Writing—review & editing. **Katia Audisio:** Data curation; Validation; Writing—original draft; Writing—review & editing. **Antonino Di Franco:** Validation; Writing—review & editing. **John H. Alexander:** Validation; Writing—review & editing. **Paul Kurlansky:** Validation; Writing—review & editing. **Andreas Boening:** Validation; Writing—review & editing. **Joanna Chikwe:** Validation; Writing—review & editing. **P.J. Devereaux:** Validation; Writing—review & editing. **Anno Diegeler:** Validation; Writing—review & editing. **Arnaldo Dimagli:** Data curation; Formal analysis; Investigation; Validation; Writing—review & editing. **Marcus Flather:** Validation; Writing—review & editing. **Andre Lamy:** Validation; Writing—review & editing. **Jennifer S. Lawton:** Validation; Writing—review & editing. **Derrick Y. Tam:** Validation; Writing—review & editing. **Wilko Reents:** Validation; Writing—review & editing. **Mohamed Rahouma:** Data curation; Formal analysis; Validation; Writing—review & editing. **Leonard N. Girardi:** Validation; Writing—review & editing. **David L. Hare:** Validation; Writing—review & editing. **Stephen E. Fremes:** Validation; Writing—review & editing. **Umberto Benedetto:** Conceptualization; Data curation; Investigation; Methodology; Project administration; Supervision; Validation; Writing—review & editing.

## Reviewer information

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