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REPORT

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The RADial artery International ALliance (RADIAL) extended follow-up study: rationale and study protocol

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Abstract

It is generally accepted that radial artery (RA) grafts have better mid-term patency rate compared to saphenous vein grafts. However, the clinical correlates of the improved patency rate are still debated. Observational studies have suggested increased survival and event-free survival for patients who receive an RA rather than a saphenous vein, but they are open to bias and confounders. The only evidence based on randomized data is a pooled meta-analysis of 6 randomized controlled trial comparing the RA and the saphenous vein published by the RADial artery International Alliance (RADIAL). In the RADIAL database, improved freedom from follow-up cardiac events (death, myocardial infarction and repeat revascularization) was found at 5-year follow-up in the RA arm. The most important limitation of the RADIAL analysis is that most of the included trials had an angiographic follow-up in the first 5 years and it is unclear whether the rate of repeat revascularization (the main driver of the composite outcome) was clinically indicated due to per-protocol angiographies. Here, we present the protocol for the long-term analysis of the RADIAL database. By extending the follow-up beyond the 5th postoperative year (all trials except 1 did not have angiographic follow-up beyond 5 years), we aim to provide data on the role of RA in coronary artery bypass surgery with respect to long-term outcomes.

Keywords: Coronary artery bypass • Myocardial revascularization • Arteries • Radial Artery Patency Study • Radial Artery Versus Saphenous Vein Patency trial

ABBREVIATIONS

ART	Arterial Revascularization Trial
CABG	Coronary artery bypass grafting
CI	Confidence interval
HR	Hazard ratio
RA	Radial artery
RADIAL	RADial artery International Alliance
RAPCO	Radial Artery Patency and Clinical Outcomes (RAPCO) trial
RAPS	Radial Artery Patency Study
RCT	Randomized controlled trial
RSVP	Radial Artery Versus Saphenous Vein Patency trial
SV	Saphenous vein

BACKGROUND AND RATIONALE

The long-term clinical effects of using the radial artery (RA) instead of the saphenous vein (SV) during coronary artery bypass surgery (CABG) surgery remain unclear [1].

At least 7 randomized controlled trials (RCTs) have compared the 2 conduits, consistently showing better mid-term patency rate for the RA when the artery is appropriately used (Table 1) [2–9]. However, most of the RCTs had primary angiographic end points and all of them were individually underpowered to explore differences in clinical outcomes. A trial-level meta-analysis pooling of 6 trials (1860 participants) suggested possible clinical benefits in terms of repeat revascularization and cardiac event in the RA arm [10], but no definitive conclusion could be drawn due to the intrinsic limitations of aggregate data analysis.

Furthermore, observational studies and meta-analyses of observational studies have reported a significant survival benefit in patients receiving the RA compared to patients receiving SV [11]. However, treatment allocation bias and other confounders, rather than biological effect, may explain those results [12].

In 2018, the RADial artery International Alliance (RADIAL) published the results of a patient-level pooled analysis of 6 RCTs comparing the patency rate of the 2 conduits [13]. RADIAL provides the first evidence of a clinical benefit, in terms of major adverse cardiac events at 5-year follow-up, with the use of the RA [hazard ratio (HR) 0.67, 95% confidence interval (CI) 0.49–0.90]. The superior clinical outcome was accompanied (and likely explained) by the lower risk of graft failure of RA conduits (HR 0.44, 95% CI 0.28–0.70). A *post hoc* analysis of the RADIAL database suggested an important role of chronic anti-spastic therapy with calcium channel blockers in patients with RA grafts [14].

Important imitations of the 5-year RADIAL analysis are:

1. The primary composite outcome of death, myocardial infarction and repeat revascularization was clearly driven by the latter. Nominal statistical significance was reached for the difference in myocardial infarction, while a non-statistically significant difference (7.5% vs 8.4%) was observed for death. For the individual components of the primary outcome, the HRs (and CIs) were 0.90 (0.59–1.41) for death, 0.72 (0.53–0.99) for myocardial infarction and 0.50 (0.40–0.63) for repeat revascularization.
2. Three of the 5 trials included in the clinical outcome analysis [Yoo, Radial Artery Patency and Clinical Outcomes (RAPCO) trial and Radial Artery Versus Saphenous Vein Patency (RSVP) trial] mandated angiographic follow-up at different intervals in the first 5 years. In absence of information on the reasons for repeat revascularization, it is possible that many of the revascularizations were not clinically driven due to the per-protocol reimaging finding non-symptomatic events.

The above issues are particularly relevant due to the recent publication of the 10-year results of the Arterial Revascularization Trial (ART) that found no differences in survival and event-free survival between patients receiving single or bilateral internal thoracic artery [15]. Important limitations of ART are the high crossover rate and the use of the RA in a high percentage of cases assigned to the single internal thoracic artery group. In a non-randomized as-treated analysis comparing patients who receive multiple arterial grafts (using either the right internal thoracic artery or the RA as the second graft) versus single arterial graft, a significant clinical benefit for the multiple arterial group was found [15].

Based on the above considerations, the RADIAL investigators decided to update the follow-up of the patients enrolled in the trials included in the 5-year RADIAL analysis in order to:

1. Evaluate the difference in the primary composite outcome, and of repeat revascularization in particular, between 5 and 10 years of follow-up (4/5 trials, all except RAPCO, no longer mandated per-protocol angiography after 5 years of follow-up).
2. Compare hard clinical outcomes (myocardial infarction and mortality) between the RA and SV arms over longer follow-up.

METHODS

Selection of the trials

A systematic literature search was performed on 3 January 2019 to identify RCTs not included in the 5-year RADIAL analysis that compared the RA and the SV at a mean follow-up of more than 2 years. No additional trials were identified. Details of the search strategy are given in Table 2.

It should be noted that the Radial Artery Patency Study (RAPS) trial used within-patient randomization and for this reason was not included in the 5-year clinical outcome analysis. As the 10-year analysis will also focus on clinical outcomes, this trial again will not be included in the 10-year analysis.

Following the approach used for the 5-year study, only the RA versus SV arms of RAPCO (RAPCO-SV) and Stand-in-Y will be included in the analysis. The arms of those trials where the experimental conduit is the right internal thoracic artery will not be included.

Overall, 5 RCTs (1036 patients) will be included in the 10-year analysis.

Follow-up update

For all the trials, updated clinical follow-up up to 10 years or to the maximal possible follow-up for each enrolled patient will be requested. Individual consent will be obtained when required by individual jurisdiction. Each individual trial's team will be responsible to obtain adequate ethic approval if needed. Follow-up will be performed by telephone interview or data linkage with relevant national data sources.

Data collection and merging

Similar to the 5-year analysis, an electronic preformatted data collection form containing core minimum data requirements will be sent to each trial team for completion and sending back to the data coordinating centre at Weill Cornell Medicine.

After receiving deidentified data at the coordinating centre, the data will be checked for quality, completion and consistency with both the 5-year analysis and with previous publications. Any issues will be resolved through direct consultation with the individual trial teams. The data elements from the 5 trials will be consolidated into a master database. All variable definitions will be similar to those used in the 5-year analysis.

Outcomes

The primary outcome will be a composite of major adverse cardiac events including death from any cause, myocardial

Table 1: Randomized controlled trials comparing the radial artery to other conduits

Trial acronym or first author	Year	Conduits compared	Sample size	Primary outcome	Other outcomes assessed	Follow-up	Main findings
RAPS Desai *et al.* [2]	2004	RA and SV	RA: 440 SV: 440	Graft patency (functional occlusion rate, defined as lack of thrombolysis in myocardial infarction flow grade 3, according to invasive angiography)	Graft patency (complete occlusion rate, assessed by invasive angiography or computed tomography angiography) Composite end point of major adverse cardiac events defined as cardiac death, non-fatal myocardial infarction and any repeat revascularization procedure	10.9 ± 4.3 months	• 8.2 % of RA and 13.6% of SV grafts were occluded (absolute difference 5.4%, 95% CI 5.0–5.8%; $P = 0.009$) • RRR of graft occlusion: 40% (95% CI 28–52%)
RAPCO Buxton *et al.* [3]	2003	Group 1: RA vs RITA (age <70 years) Group 2: RA vs SV (age ≥70 years)	Group 1 (RA: 140, RITA: 145) Group 2 (RA: 73, SV: 80)	Grafts patency	All-cause mortality Cardiac event-free survival (defined as survival with freedom from myocardial infarction, percutaneous intervention or reoperation)	5 years	Graft patency estimates: • 0.95 (95% CI 0.85–0.99) in 39 RAs vs 1.0 in 29 RITAs ($P = 0.4$) in group 1 • 0.86 (95% CI 0.67–0.99) in 24 RA vs 0.95 (95% CI 0.83–0.99) in 22 SV ($P = 0.5$) in group 2 Cardiac event free survival estimates: • 0.91 (95% CI 0.76–0.99) for the RA vs 0.82 (95% CI 0.63–0.99) for the RITA ($P = 0.7$) in group 1 • 0.84 (95% CI 0.64–0.99) for the RA vs 0.89 (95% CI 0.72–0.99) for the SV ($P = 0.9$) in group 2
Petrovic *et al.* [4]	2015	RA vs SV	RA: 100 SV: 100	Composite of cardiovascular mortality, non-fatal myocardial infarction and need for repeat myocardial revascularization (either surgical or percutaneous)		8 years	• No significant difference in survival between RA and SV, with 12 deaths in each group during the study period (log rank = 0.01, $P = 0.979$) • No difference in long-term composite outcome between the groups (log rank = 0.450, $P = 0.509$) • No difference in patency between RA group: patency rate 92% andSV group: patency rate 86% ($P = 0.67$)
Song *et al.* [5]	2012	RA vs SV	RA: 35 SV: 25	Graft patency	Early clinical outcomes: in-hospital mortality, atrial fibrillation, acute renal failure, reoperation due to postoperative bleeding, low cardiac output syndrome, mediastinitis, pulmonary complications and prolonged hospital stay	Postoperative day 7 and 1 year	• Early patency was 100% and 99.1% for the SV and RA groups, respectively ($P = 0.412$) • 1-Year patency was 94.7% and 97.4% for SV and RA groups ($P = 0.437$)

Continued

Table 1: Continued

Trial acronym or first author	Year	Conduits compared	Sample size	Primary outcome	Other outcomes assessed	Follow-up	Main findings
Nasso *et al.* [6]	2009	Group 1: Y graft: *in situ* LITA-LAD and RITA to secondary targets with or without SV Group 2: *In situ* RITA-LAD + *in situ* LITA to secondary targets with or without SV Group 3. *In situ* LITA-LAD + RA to secondary target Group 4: *In situ* LITA-LAD + SV to revascularize all non-LAD targets	Group 1 (LITA-LAD + RITA): 201 Group 2 (RITA-LAD + LITA): 198 Group 3 (LITA-LAD + RA): 202 Group 4 (LITA-LAD + SV): 202	In-hospital outcomes: mortality rate, morbidity 2-Year freedom from all-cause death and adverse cardiac event-free survival (including cardiac death, acute myocardial infarction, recurrent angina, graft occlusion at coronary angiography, redo coronary surgery or percutaneous transluminal coronary angioplasty)		24.1 ± 9.8 months	At 2 years: • Overall survival was not significantly different among groups ($P = 0.59$) • Cardiac event-free survival was significantly better in patients receiving 2 arterial grafts vs control subjects ($P < 0.0001$), even among elderly patients ($P = 0.022$) • The 3 investigated strategies using 2 arterial conduits were similar concerning early- and mid-term results
RSVP Collins *et al.* [7]	2008	RA vs SV	RA: 82 SV: 60	Graft patency	Survival	5 years	Graft occlusion occurred in 6/44 SV grafts and 1/59 RA grafts, corresponding to patency rates of 86.4% and 98.3% ($P = 0.04$) and an absolute difference of 11.9% (95% CI 5.6–18.2)
VA trial Goldman *et al.* [8]	2011	RA vs SV	RA: 366 SV: 367	Graft patency at 1 year	Graft patency at 1 week after CABG, myocardial infarction, stroke, repeat revascularization and death	1 year	No significant difference in graft patency at 1 year after CABG: RA: 238/266; 89%; 95% CI 86–93% SV: 239/269; 89%; 95% CI 85–93% Adjusted OR 0.99, 95% CI 0.56–1.74; $P = 0.98$)
Dreifaldt *et al.* [9]	2013	No touch SV vs RA	NT SV (left) and RA (right): 47 NT SV (right) RA (left): 52	Graft patency		36 months (range 12–69)	• Patent graft rates were 93/99 (94%) for NT SV vs 81/99 (82%) for RA • OR for patency NT SV vs RA (OR 3.4, 95% CI 1.3–9.1; $P = 0.013$) • The RA was anastomosed to target with stenosis <70% in 31% of the cases and <90% in 69% of the cases

CABG: coronary artery bypass grafting; CI: confidence interval; LAD: left anterior descending artery; LITA: left internal thoracic artery; NT: no-touch; OR: odds ratio; RA: radial artery; RITA: right internal thoracic artery; RRR: relative risk reduction; SV: saphenous vein; VA: veteran affairs.

Table 2: Search strategy

1. Radial Artery/
2. (radial arter* or arteria radialis or radialis artery).tw.
3. 1 or 2
4. Saphenous Vein/
5. (Saphenous or SVG or saphena vein or saphenous venos system or vena saphena).tw.
6. 4 or 5
7. Coronary Artery Bypass/
8. (aorta adj2 bypass).tw.
9. CABG.tw.
10. (aortic coronary bypass or aorticocoronary anastomosis).tw.
11. (aorto coronary adj2 (bypass or graft)).tw.
12. (aortocoronary adj2 (anastomosis or bypass or shunt or graft)).tw.
13. (coronary adj2 (bypass or graft)).tw.
14. (Total arterial revascularization or total arterial revascularisation or Multiple arterial revascularization or multiple arterial revascularisation).tw.
15. or/7–14
16. 3 and 6 and 15

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infarction and repeat revascularization. The secondary outcome will be a composite of death and myocardial infarction. For all the events, individual trial definitions will be used.

Each component of the composite outcomes will also be analysed separately, but not formally tested.

Prespecified subgroup analyses will be performed by age, gender, diabetes status, preoperative history of myocardial infarction, use of calcium channel blockers, left ventricular ejection fraction, preoperative renal function and RA target vessel.

Statistical analysis

Baseline and intraoperative characteristics in the 2 groups will be reported as counts and percentages for categorical variables and as means and standard deviations (or median and interquartile range) for continuous variables. Parametric or non-parametric tests will be used to compare the 2 groups, as appropriate. A comparison of baseline characteristics will also be done between patients who were lost to follow-up and those included in the analysis to ensure that patients with follow-up are representative of the parent cohorts.

Descriptively, outcomes will be reported as numbers, cumulative incidence and linearized event rates per 1000 patient-years to account for different follow-up duration across individual trials. Cumulative incidence of non-fatal events will be determined with death as a competing risk. The primary analysis will be performed according to the intention-to-treat principle (based on randomization), assuming that the percentage of patients lost to follow-up is less than 10%. If the percentage of patients lost to follow-up is >10%, a per-protocol analysis will be used as the main analysis. Treatment effect on outcomes of interest will be estimated using a mixed-effect Cox regression model, with treatment allocation included as fixed effect and trial identifiers included as random effect. Treatment effects will be presented as HRs and 95% CIs. The proportional hazards assumptions will be verified using Schoenfeld residuals. If the proportional hazards model is violated, it will be explored if it is due to the cessation of protocol-mandated angiography through its impact on revascularization.

To better understand the impact of protocol-mandated angiography on the difference in revascularization rates between the 2 arms, a secondary analysis of this end point will be performed with protocol-mandated angiography as a time-varying covariable. Specifically, piecewise HRs will be fit for the period under protocol-mandated angiography and the period when there is no protocol-mandated angiography. If it appears as the HR changes over these periods, the primary end point will be reanalysed using piecewise HRs.

Additional analyses for the primary outcome will include subgroup analyses to assess whether the effect of treatment is similar across subgroups of interest. The results will be displayed as a forest plots. Non-linear relationship between age and treatment effect will be investigated by comparing model fitting with age used as a linear term versus with age used as a spline function with an increasing number of knots. A potential age cut-off for the loss of benefit with the RA will be evaluated with non-parametric computation of bootstrap pointwise confidence limits across a range of ages.

As sensitivity analysis, the treatment effect on the primary outcome will be re-estimated according to the as-treated principle (based on received treatment). In addition, the analysis will be repeated using a 2-stage approach where a beta-coefficient with relative standard error for the treatment effect will be obtained for each individual trial using a Cox regression model. Treatment effect estimates across individual trials will be pooled in a second step using generic inverse variance method with a random effect.

An influence analysis will be used to assess the influence of individual trials on the final estimate.

The SV group will be used as the reference in all analyses. A fixed-order sequential testing method with the primary outcome tested first will be used to test the primary and secondary outcomes.

All *P*-values will be 2-sided. *P*-values of <0.05 will be deemed statistically significant. No significance testing will be done for subgroup analyses and for the individual components of the composite outcomes. For these analyses, we will only generate estimates of treatment effects and corresponding 95% CIs. Statistical analyses will be performed with R software, version 3.2.3 (R Foundation) and the following packages: survival (https://CRAN.R-project.org/package=survival), coxme (https://CRAN.R-project.org/package=coxme), meta (https://cran.r-project.org/doc/Rnews/Rnews_2007-3.pdf), ggplo2 (http://ggplot2.org) and forestplot (https://CRAN.R-project.org/package=forestplot).

CONCLUSION

Extension of the follow-up beyond the fifth postoperative year will likely shed new light on the clinical consequences of the use of the RA instead of the SV for CABG.

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Conflict of interest: Giuseppe Biondi-Zoccai has consulted for Abbott Vascular and Bayer. Neil Moat is an employee of Abbott, Santa Clara, USA. All other authors have nothing to disclose.

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