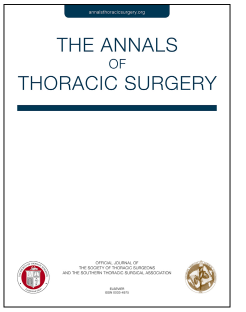
Journal Pre-proof



Angiographic outcome of coronary artery bypass grafts: Radial Artery Database International Alliance

Mario Gaudino, MD, Umberto Benedetto, MD, Stephen E. Fremes, MD, David L. Hare, MD, Philip Hayward, MD, Neil Moat, MD, Marco Moscarelli, MD, Antonino Di Franco, MD, Giuseppe Nasso, MD, Miodrag Peric, MD, Ivana Petrovic, MD, Peter Collins, MD, Carolyn M. Webb, PhD, John D. Puskas, MD, Giuseppe Speziale, MD, Kyung Jong Yoo, MD, Leonard N. Girardi, MD, David P. Taggart, MD, for the RADIAL Investigators

PII: S0003-4975(19)31226-3

DOI: https://doi.org/10.1016/j.athoracsur.2019.07.010

Reference: ATS 32930

To appear in: *The Annals of Thoracic Surgery*

Received Date: 10 February 2019

Revised Date: 4 June 2019

Accepted Date: 1 July 2019

Please cite this article as: Gaudino M, Benedetto U, Fremes SE, Hare DL, Hayward P, Moat N, Moscarelli M, Di Franco A, Nasso G, Peric M, Petrovic I, Collins P, Webb CM, Puskas JD, Speziale G, Yoo KJ, Girardi LN, Taggart DP, for the RADIAL Investigators, Angiographic outcome of coronary artery bypass grafts: Radial Artery Database International Alliance, *The Annals of Thoracic Surgery* (2019), doi: https://doi.org/10.1016/j.athoracsur.2019.07.010.

Angiographic outcome of coronary artery bypass grafts: Radial Artery Database International Alliance

Mario Gaudino MD[1*], Umberto Benedetto MD[2*], Stephen E Fremes MD[3], David L Hare MD[4,5], Philip Hayward MD[4], Neil Moat MD[6], Marco Moscarelli MD[7], Antonino Di Franco MD[1], Giuseppe Nasso MD[7], Miodrag Peric MD[8], Ivana Petrovic MD[8], Peter Collins MD[9], Carolyn M Webb PhD[9], John D Puskas MD[10], Giuseppe Speziale MD[7], Kyung Jong Yoo MD[11], Leonard N Girardi MD[1], David P Taggart MD[12] for the RADIAL Investigators†.

†A complete list of investigators of the RADIAL (Radial Artery Database International ALliance) project is provided in the **Supplementary Material.**

[1]*Department of Cardiothoracic Surgery, Cornell Medicine, New York, US*
[2]*Bristol Heart Institute, Bristol, UK*
[3]*Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada*
[4]*University of Melbourne, Melbourne, Australia*
[5]*The Austin Hospital, Melbourne, Vic, Australia*
[6]*Royal Brompton & Harefield Trust, London, UK*
[7]*Anthea Hospital, Bari, Italy*
[8]*Dedinje Cardiovascular Institute and Belgrade University School of Medicine, Belgrade, Serbia*
[9]*National Heart & Lung Institute, Imperial College London, London, UK*
[10]*Icahn School of Medicine at Mount Sinai, New York City, US*
[11]*Yonsei University College of Medicine, Seoul, Korea*
[12]*University of Oxford, Oxford, UK*

*Drs Gaudino and Benedetto contributed equally to this work.

Presented at the 2018 Society of Thoracic Surgeons Annual Meeting – San Diego

Running head: Coronary graft patency

Word count: 3302

Corresponding Author
Mario Gaudino, MD
Department of Cardio-Thoracic Surgery, Weill Cornell Medicine
525 E 68th St
New York, NY 10065
Email: mfg9004@med.cornell.edu

Abstract

Background: We used a large patient-level dataset including six angiographic randomized trials (RCTs) on coronary artery bypass conduits to explore incidence and determinants of coronary graft failure.

Methods: Patient-level angiographic data of six RCTs comparing long-term outcomes of the radial artery and other conduits were joined. Primary outcome was graft occlusion at maximum follow-up. The analysis was divided as follows: 1) left anterior descending coronary (LAD) distribution, 2) non-LAD distribution (circumflex and right coronary artery). To identify predictors of graft occlusion, mixed model multivariable Cox regression including all baseline characteristics with stratification by individual trials was used.

Results: 1091 patients and 2281 grafts were included (921 left internal mammary arteries, 74 right internal mammary arteries, 710 radial artery and 576 saphenous veins; all left internal mammary arteries were used on the LAD, the other conduits were used on the non-LAD distribution; mean angiographic follow up: 65±29 months). Occlusion rate was 2.3%, 13.5%, 9.4%, 17.5% for the left internal mammary arteries, right internal mammary arteries, radial artery and saphenous veins, respectively. At multivariable analysis type of conduit used, age, female gender, left ventricular ejection fraction<50% and use of the Y graft were significantly associated with graft occlusion in the non-LAD distribution.

Conclusions: Our analyses showed that failure of the left internal mammary arteries to LAD bypass is a very uncommon event. For the non-LAD distribution, the non-use of radial artery, age, female gender, left ventricular ejection fraction<50% and use of the Y graft configuration were significantly associated with mid-term graft failure.

Key words: CABG, patency, radial artery

Although the relationship between graft status and clinical outcome is less clear than usually accepted,(1) it seems reasonable to say that the primary goal of coronary bypass grafting (CABG) operations is long-term patency of the bypass grafts.

Despite the five decades history of CABG surgery and the fact that it is the most common cardiac surgery procedure performed in adults, the current evidence on the frequency of and risk factors determining graft occlusion is surprisingly limited.

The great majority of observational series have major biases and limitations in particular with regards to the completeness of the angiographic follow-up. On the other hand angiographic randomized trials (RCTs) have minimal risk of bias and much higher completeness of follow-up, but taken individually have usually a sample size inadequate to allow a meaningful exploration of the determinants of graft patency.

In this manuscript we use a large patient-level dataset including six angiographic RCTs of CABG conduits to explore the incidence and determinants of coronary graft failure.

Material and Methods

Dataset

Details of the Radial Artery Database International Alliance (RADIAL) project have previously been published (2). The list of the RADIAL investigators is enclosed in **Supplementary Table 1**. Briefly, RADIAL is a patient-level database pooling six RCTs comparing the long-term outcomes of the radial artery (RAD) and other conduits at a mean follow-up ≥2 years. The 6 RCTs included are: the Radial Artery Patency and Clinical Outcomes (RAPCO, groups 1 and 2), the Radial Artery Patency Study (RAPS), the Radial Artery Versus Saphenous Vein Patency Study (RSVP), Petrovic, Stand-in-Y and Yoo trials.(3–8)

In the present analysis, we included all available individual angiographic patient level data from all the angiographic trials. As Petrovic's trial had no angiographic follow-up, it was excluded from the present analysis.

Outcomes

The primary outcome was graft occlusion at maximum follow-up. Graft angiographic status was graded according to the Fitzgibbon classification (9). Grade A and B were considered patent and grade O occluded.

Statistical analysis

Continuous variables were tested for normality and were reported as means and standard deviations or median and interquartile range (IQR). The t-test or Wilcoxon–Mann–Whitney test were used to compare continuous variables. Categorical variables were reported as counts and percentages and compared with Chi-squared test. Time-to-event outcomes were reported as a cumulative incidence using Kaplan Meier estimates and curves were compared using log-rank test.

Due to the differences in target vessel characteristics and conduits used, the analysis for graft occlusion was divided as follows: 1) left anterior descending coronary (LAD) distribution, 2) non-LAD distribution (including the circumflex and the right coronary artery [LCX and RCA]).

To identify predictors of graft occlusion, mixed model multivariable Cox regression including all baseline characteristics with stratification by individual trials was used. Covariates included in the Cox models were: age, gender, diabetes, previous myocardial infarction (MI), surgical priority, renal insufficiency, left ventricular ejection fraction (LVEF), target vessel, location of proximal anastomosis, number of grafts per patient and off-pump surgery (OPCABG). Treatment effect was reported as hazard ratios (HR) with 95% confidence intervals (CI). The proportional hazard assumptions were verified using Schoenfeld residuals. R version 3.1.2 (2014-10-31) was used for all statistical analyses and p value significance was set at 0.05.

Results

Overall, 1091 patients and 2281 grafts were included in the angiographic analysis, representing 71.8% of the total number of the patients enrolled in the five RCTs (1091/1519).

The mean age was 64.9±9.5 years, there were 825 males (75.6%), 329 cases were diabetics (30.2%), 349 (32.0%) had previous MI, and 170 (15.6%) had LVEF <50%. The mean number of grafts per patient was 3.4±0.7. Demographics of the study population are reported in **Table 1**.

There were 921 left internal mammary arteries (LIMA), 74 right internal mammary arteries (RIMA), 710 RAD and 576 saphenous veins (SVG). All LIMA were used on the LAD, while the other conduits were used on the non-LAD distribution.

The mean angiographic follow up was 65±29 months, with small variations for the different conduits. The occlusion rate was 2.3% (21/921) for the LIMA, 13.5% (10/74) for the RIMA, 9.4% (67/710) for the RAD and 17.5% (101/576) for the SVG (see **Table 2**). Baseline features and angiographic follow-up data stratified for the second conduit received are provided in **Supplementary Table 2**; Occlusion rates stratified according to the type of second conduit and target vessel are shown in **Supplementary Table 3**.

LAD analysis

Age, previous MI, surgical priority and LVEF <50% were significantly different between patients with open and occluded graft (**Supplementary Table 4**). However, at multivariable regression none of these variables was significantly associated with graft occlusion (**Table 3**).

Non-LAD analysis

At multivariable analysis the type of conduit used, age ≥ 75 years, female gender, LVEF <50% and use of the Y graft technique were significantly associated with graft occlusion (**Table 4**).

The RAD has significantly better patency rate than all the other conduits (**Figure 1**). This was confirmed for both the LCX and RCA distribution (**Figure 2**).

The better patency rate of the RAD was confirmed for both genders, although for women the level of statistical significance was higher (**Figure 3**).

The use of the Y graft technique was associated with a significantly higher occlusion rate (**Figure 4**). This was mainly driven by the lower patency rate of RAD Y grafts; for the SVG the difference between aorta-anastomosed and Y grafts did not reach statistical significance (**Supplementary Figure 1**). Occlusion rates stratified for the type of proximal anastomosis are provided in **Supplementary Table 5**.

Comment

With 1091 patients and 2281 grafts at a mean follow-up of 65±29 months and a re-angiography rate of almost 72% RADIAL is one of the largest and the most complete coronary graft angiographic databases. The results of our analysis show that the failure of the LIMA to LAD bypass is a very uncommon event, so that even with a large patient sample, it was not possible to define independent risk factors for it.

For the non-LAD distribution, the non-use of the RAD, age ≥ 75 years, female gender, LVEF <50% and use of the Y graft configuration were significantly associated with mid-term graft failure. Published observational angiographic databases on coronary graft failure are usually limited by the low rate of angiographic follow-up and the selection bias due to the fact that symptomatic patients are more likely to be submitted to re-angiography. Most of the available angiographic series on graft patency have a re-angiography rate between 20 and 40% (10,11) and are of often limited to cases of angina recurrence. The Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT) IV trial, the second largest prospective angiographic database after RADIAL, had an angiographic follow-up rate of 51%.(12) The low re-angiography rate and the fact that patients who missed follow up are likely to be different from patients who underwent re-angiography make extrapolation of the published results to the overall CABG population unreliable.

On the other hand, most of the included angiographic RCTs had a good re-angiography rate, and by pooling the five angiographic RCTs, this post-hoc analysis of RADIAL was aimed to overcome the power limitations of the individual studies.

The better patency rate of the RAD compared to the SVG has been firmly established.(2) We were able to confirm that the RAD outperforms the SVG for both the circumflex and right coronary distribution and in both genders (although the difference was larger in women). This is concordant with observational series with a high re-angiography rate.(13)

The RADIAL Database was not designed to compare the RIMA with any conduit. Although in this series the patency rate of the RITA is lower than reported, this analysis is clearly underpowered and should be viewed with skepticism.

Our finding of an increased failure rate for Y grafts is in contrast with those of other authors.(14) However, it is known that Y grafts (in particular using the RAD) are more sensitive to the detrimental effect of competitive flow (15) and this may be a potential mechanism behind their higher failure rate.

This study has important limitations. While the original studies were RCTs, this analysis shares the problems of observational series. Hidden and unmeasured confounders may persist despite statistical adjustment. Differences in surgical expertise, and follow-up angiographic protocols among trials may have influenced our findings.

Despite these limitations, RADIAL is one of the largest and most complete angiographic databases on CABG conduits. We confirm that failure of the LIMA to LAD bypass is a very uncommon event. For the non-LAD distribution, the non-use of RAD, age ≥75 years, female gender, LVEF <50% and use of the Y graft configuration were significantly associated with mid-term graft failure. These patency data should inform future surgical planning and clinical decision making.

References

1. Halabi AR, Alexander JH, Shaw LK, et al. Relation of early saphenous vein graft failure to outcomes following coronary artery bypass surgery. Am J Cardiol 2005;96:1254–9.

2. Gaudino M, Benedetto U, Fremes S, et al. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. N Engl J Med 2018;378:2069–77.

3. Buxton BF, Raman JS, Ruengsakulrach P, et al. Radial artery patency and clinical outcomes: five-year interim results of a randomized trial. J Thorac Cardiovasc Surg 2003;125:1363–71.

4. Deb S, Cohen EA, Singh SK, et al. 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.

5. Collins P, Webb CM, Chong CF, Moat NE, Radial Artery Versus Saphenous Vein Patency (RSVP) Trial Investigators. Radial artery versus saphenous vein patency randomized trial: five-year angiographic follow-up. Circulation 2008;117:2859–64.

6. Petrovic I, Nezic D, Peric M, et al. Radial artery vs saphenous vein graft used as the second conduit for surgical myocardial revascularization: long-term clinical follow-up. J Cardiothorac Surg 2015;10:127.

7. Nasso G, Coppola R, Bonifazi R, Piancone F, Bozzetti G, Speziale G. Arterial revascularization in primary coronary artery bypass grafting: Direct comparison of 4 strategies--results of the Stand-in-Y Mammary Study. J Thorac Cardiovasc Surg 2009;137:1093–100.

8. Song S-W, Sul S-Y, Lee H-J, Yoo K-J. Comparison of the radial artery and saphenous vein as composite grafts in off-pump coronary artery bypass grafting in elderly patients: a randomized controlled trial. Korean Circ J 2012;42:107–12.

9. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. J Am Coll Cardiol 1996;28:616–26.

10. Ruttmann E, Dietl M, Feuchtner GM, et al. Long-term clinical outcome and graft patency of radial artery and saphenous vein grafts in multiple arterial revascularization. J Thorac Cardiovasc Surg 2018; pii: S0022-5223(18)32929-5. doi: 10.1016/j.jtcvs.2018.10.135.

11. Tatoulis J, Buxton BF, Fuller JA. The right internal thoracic artery: the forgotten conduit--5,766 patients and 991 angiograms. Ann Thorac Surg 2011;92:9–15; discussion 15-17.

12. Harskamp RE, Alexander JH, Ferguson TB, et al. Frequency and Predictors of Internal Mammary Artery Graft Failure and Subsequent Clinical Outcomes: Insights From the Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT) IV Trial. Circulation 2016;133:131–8.

13. Gaudino M, Tondi P, Benedetto U, et al. Radial Artery as a Coronary Artery Bypass Conduit: 20-Year Results. J Am Coll Cardiol 2016;68:603–10.

14. Royse AG, Brennan AP, Ou-Young J, Pawanis Z, Canty DJ, Royse CF. 21-Year Survival of Left Internal Mammary Artery-Radial Artery-Y Graft. J Am Coll Cardiol 2018;72:1332–40.

15. Gaudino M, Alessandrini F, Pragliola C, et al. Effect of target artery location and severity of stenosis on mid-term patency of aorta-anastomosed vs. internal thoracic artery-anastomosed radial artery grafts. Eur J Cardiothorac Surg 2004;25:424–8.

Table 1. Demographics of the study population.

N. of included patients	1091 (/1519 = 71.8%)
Age, years (SD)	64.96 (9.48)
Male, n (%)	825 (75.6)
Diabetes, n (%)	329 (30.2)
Previous MI	349 (32.0)
LVEF <50%	170 (15.6)
Renal Dysfunction	64 (5.9)
Elective	874 (80.1)
OPCABG, n (%)	43 (3.9)
Number of grafts, mean (SD)	3.4 (0.7)
Grafts	2281
- RAD	710
- RIMA	74
- SVG	576
- LIMA	921

SD, standard deviation; OPCABG, off-pump coronary artery bypass grafting; RAD, radial artery, RIMA, right internal mammary artery; LIMA, left internal mammary artery; SVG, saphenous vein graft.
Renal dysfunction was defined as preoperative serum creatinine >1.5 mg/dl.(2)

Table 2. Occlusion rates.

	RAD	RIMA	SVG	LIMA
Number	710	74	576	921
Angio-follow-up duration in months, mean (SD)	67.2 (30.9)	61.6 (6.16)	70.8 (30.2)	64.1 (28.7)
Occluded graft, n (%)	67 (9.4)	10 (13.5)	101 (17.5)	21 (2.3)

SD, standard deviation; RAD, radial artery, RIMA, right internal mammary artery; LIMA, left internal mammary artery; SVG, saphenous vein graft.

Table 3. Risk factors for left internal thoracic artery to left anterior descending occlusion.

Variable		HR (univariable)	HR (multivariable)
Age, mean (SD)		1.00 (0.95-1.06, p=0.86)	-
Gender	Female	-	-
	Male	1.08 (0.36-3.21, p=0.89)	-
Diabetes	No	-	-
	Yes	1.29 (0.54-3.08, p=0.56)	-
Prior MI	No	-	-
	Yes	2.57 (1.07-6.14, p=0.03)	2.38 (0.99-5.68, p = 0.053)
Elective surgery	No	-	-
	Yes	0.50 (0.21-1.18, p=0.11)	-
Renal insufficiency	No	-	-
	Yes	0.74 (0.10-5.64, p=0.77)	-
LVEF <50%	No	-	-
	Yes	1.40 (0.57-3.44, p=0.47)	-
Number of grafts, mean (SD)		1.66 (0.98-2.82, p=0.06)	1.60 (0.92-2.77, p = 0.10)
OPCABG	No	-	-
	Yes	0.00 (0.00-Inf, p=0.99)	-

LVEF, left ventricular ejection fraction; MI, myocardial infarction; OPCABG, off-pump coronary artery bypass grafting; SD, standard deviation.

Table 4. Risk factors for graft occlusion in the non-left anterior descending distribution.

Variable		HR (univariable)	HR (multivariable)
Conduit	RAD	-	-
	RIMA	2.83 (1.43-5.59, p=0.003)	3.17 (1.57-6.38, p=0.001)
	SVG	2.02 (1.49-2.76, p<0.001)	2.08 (1.52-2.84, p<0.001)
Age	<75	-	-
	≥75	4.05 (2.57-6.40, p<0.001)	3.43 (2.08-5.64, p<0.001)
Gender	Female	-	-
	Male	0.56 (0.41-0.77, p<0.001)	0.59 (0.43-0.83, p=0.002)
Diabetes	No	-	-
	Yes	1.21 (0.89-1.63, p=0.22)	-
Prior MI	No	-	-
	Yes	1.07 (0.79-1.45, p=0.66)	-
Elective surgery	No	-	-
	Yes	1.27 (0.89-1.81, p=0.19)	-
Renal insufficiency	No	-	-
	Yes	1.27 (0.67-2.41, p=0.47)	-
LVEF <50%	No	-	-
	Yes	0.59 (0.41-0.84, p=0.003)	0.68 (0.48-0.98, p=0.03)
Target vessel	LCX	-	-
	RCA	1.03 (0.77-1.38, p=0.85)	-
Proximal	aorta	-	-
	Y graft	5.19 (2.62-10.30, p<0.001)	3.96 (1.43-10.97, p=0.008)
Number of grafts	Mean (SD)	0.80 (0.64-0.99, p=0.04)	-
OPCABG	No	-	-
	Yes	7.54 (3.05-18.62, p<0.001)	0.61 (0.15-2.44, p=0.48)

LCX, left circumflex coronary artery; LIMA, left internal mammary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OPCABG, off-pump coronary artery bypass grafting; RAD, radial artery; RCA, right coronary artery; RIMA, right internal mammary artery; SD, standard deviation; SVG, saphenous vein graft.

Figure Legends

Figure 1. Occlusion rate by conduit. RAD, radial artery; RIMA, right internal mammary artery; SVG, saphenous vein graft.

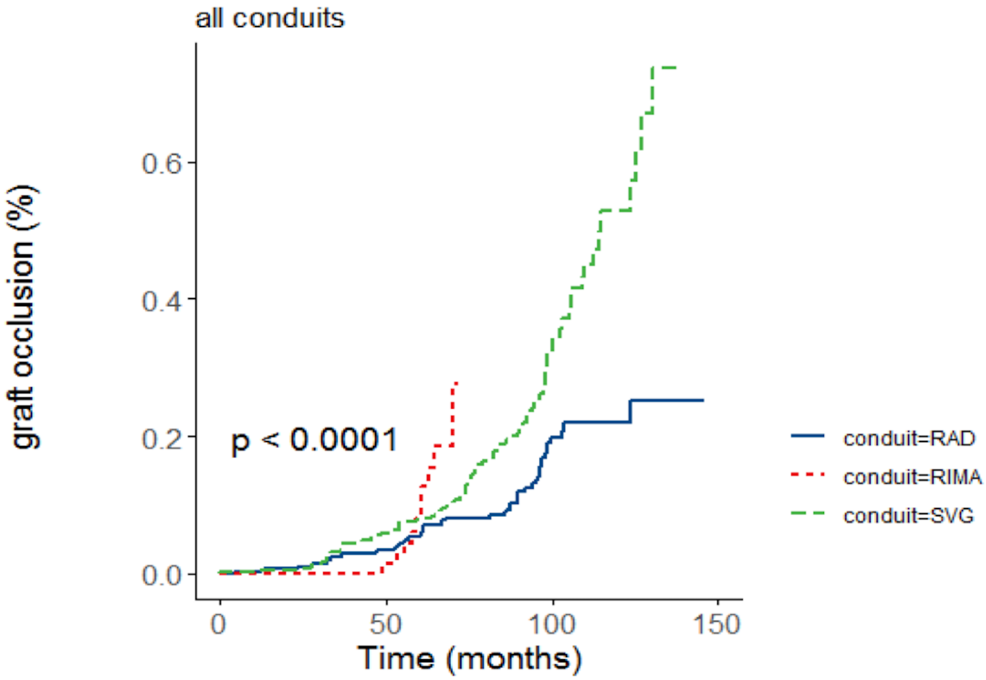
Figure 2. Occlusion rate by target vessel and conduit. LCX, left circumflex coronary artery; RAD, radial artery; RCA, right coronary artery; RIMA, right internal mammary artery; SVG, saphenous vein graft.

Figure 3. Occlusion rate by gender and conduit. RAD, radial artery; RIMA, right internal mammary artery; SVG, saphenous vein graft.

Figure 4. Occlusion rate by site of proximal anastomosis.

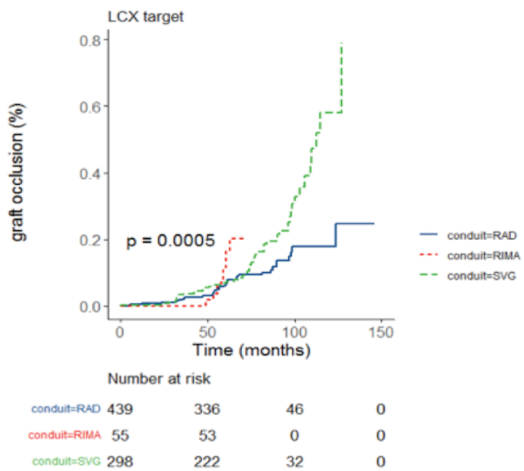
List of the abbreviations

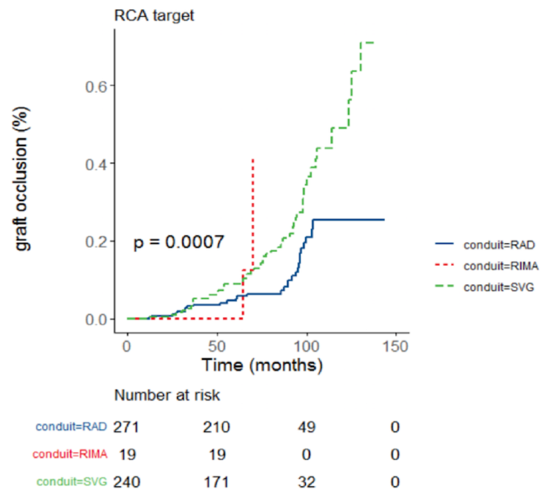
CABG, coronary bypass grafting
CI, confidence intervals
HR, hazard ratios
IQR, interquartile range
LAD, left anterior descending coronary
LCX, circumflex coronary artery
LIMA, left internal mammary arteries
LVEF, left ventricular ejection fraction
MI, myocardial infarction
OPCABG, off-pump coronary artery bypass grafting
PREVENT, Project of Ex-vivo Vein Graft Engineering via Transfection
RAD, radial artery
RADIAL, Radial Artery Database International ALliance
RAPCO, Radial Artery Patency and Clinical Outcomes
RAPS, Radial Artery Patency Study
RCA, right coronary artery
RCTs, randomized trials
RIMA, right internal mammary arteries
RSVP, Radial Artery Versus Saphenous Vein Patency Study
SVG, saphenous vein graft

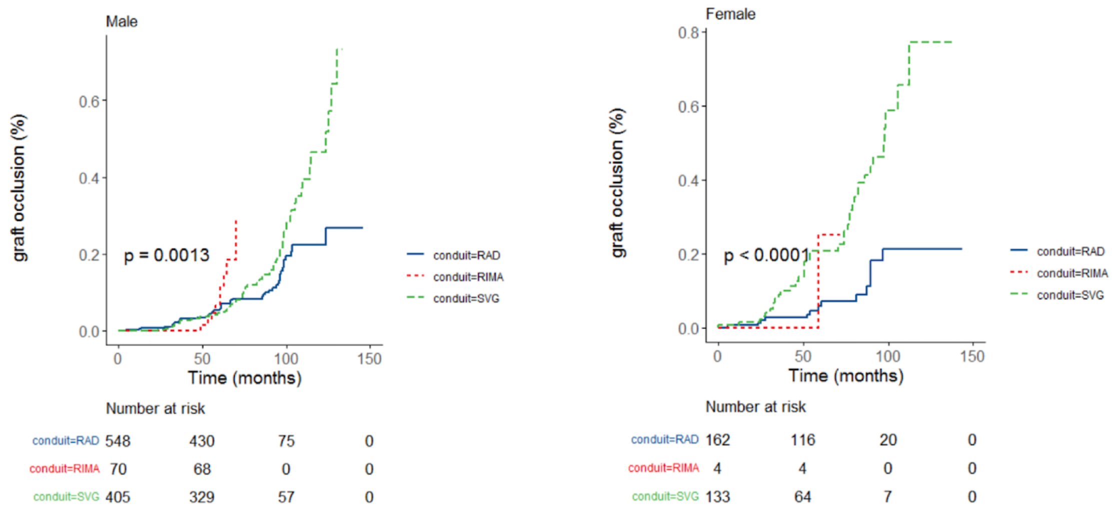


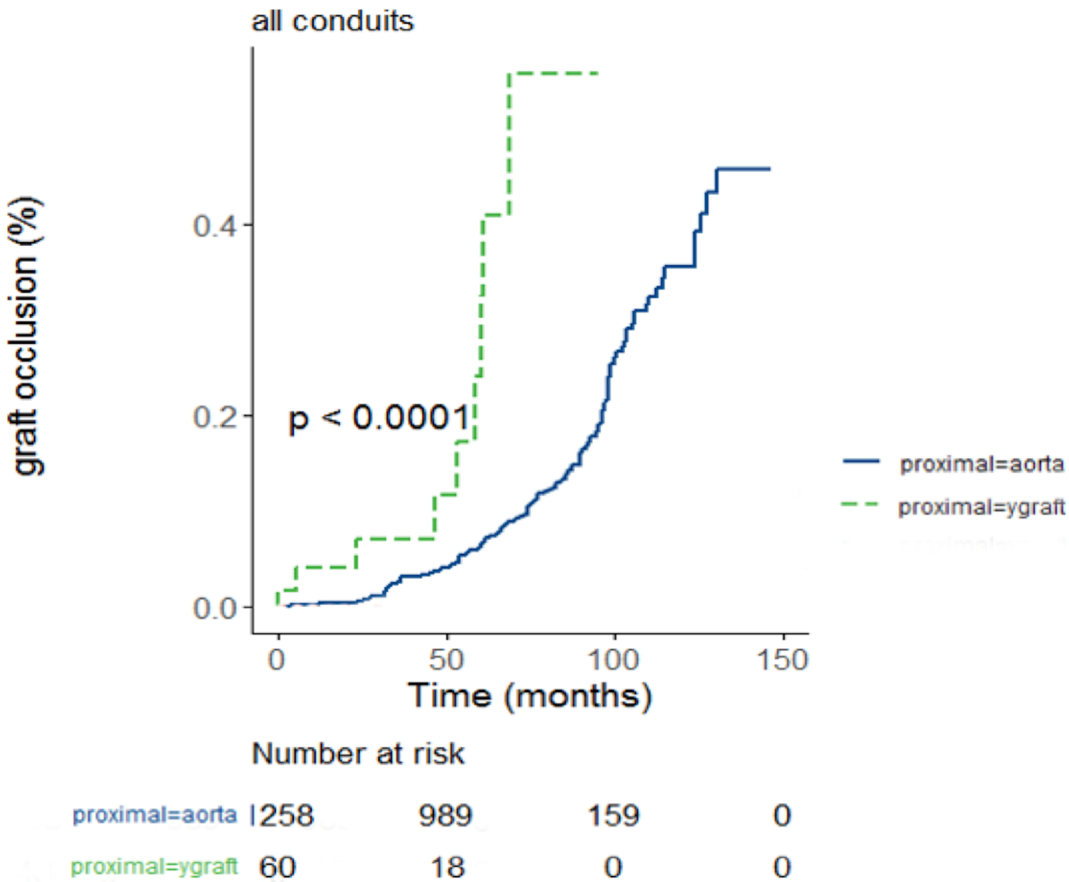
Number at risk

conduit=RAD	710	546	95	0
conduit=RIMA	74	72	0	0
conduit=SVG	538	393	64	0


LCX target
graft occlusion (%)
0.8
0.6
0.4
0.2
0.0
p = 0.0005
0
50
100
150
Time (months)
conduit=RAD
conduit=RIMA
conduit=SVG
Number at risk
conduit=RAD 439 336 46 0
conduit=RIMA 55 53 0 0
conduit=SVG 298 222 32 0


RCA target
graft occlusion (%)
0.6
0.4
0.2
0.0
p = 0.0007
0
50
100
150
Time (months)
conduit=RAD
conduit=RIMA
conduit=SVG
Number at risk
conduit=RAD 271 210 49 0
conduit=RIMA 19 19 0 0
conduit=SVG 240 171 32 0


Male
graft occlusion (%)
p = 0.0013
Time (months)
conduit=RAD
conduit=RIMA
conduit=SVG
Number at risk
conduit=RAD 548 430 75 0
conduit=RIMA 70 68 0 0
conduit=SVG 405 329 57 0
Female
graft occlusion (%)
p < 0.0001
Time (months)
conduit=RAD
conduit=RIMA
conduit=SVG
Number at risk
conduit=RAD 162 116 20 0
conduit=RIMA 4 4 0 0
conduit=SVG 133 64 7 0


all conduits
graft occlusion (%)
0.4
0.2
0.0
p < 0.0001
0
50
100
150
Time (months)
proximal=aorta
proximal=ygraft
Number at risk
proximal=aorta 1258 989 159 0
proximal=ygraft 60 18 0 0