

Coronary Artery Bypass Graft Surgery Using the Radial Artery as a Secondary Conduit Improves Patient Survival

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Background—The clinical benefits of the left internal thoracic artery–to–left anterior descending coronary artery graft are well established in coronary artery bypass graft surgery (CABG). However, limited data are available regarding the long-term outcome of the radial artery (RA) as a secondary conduit over the established standard of the saphenous venous graft.

Methods and Results—We compared the 12-year survival outcome in a set of propensity-matched CABG patients who received either the RA or the saphenous vein as a secondary conduit. A multivariable logistic regression that included 18 baseline characteristics was used to define the propensity of receiving an RA graft. The propensity model resulted in 260 matched pairs who underwent first-time isolated CABG from 1996 to 2001 with similar preoperative characteristics (C statistic=0.86). The cumulative 12-year survival estimated by use of the Kaplan–Meier method was higher for the RA graft patients (hazard ratio 0.76; $P=0.03$). This survival advantage was especially significant in diabetics ($P=0.005$), in women ($P=0.02$), and in the elderly ($P=0.04$.) The protective effect appeared beginning at year 5 post surgical intervention.

Conclusion—The RA as a secondary conduit provided superior long-term survival after CABG, especially in diabetic patients, women, and the elderly. This effect was most pronounced >5 years after surgery. (*J Am Heart Assoc.* 2013;2:e000266 doi: 10.1161/JAHA.113.000266)

Key Words: coronary artery disease • radial artery graft • revascularization

With the use of the left internal thoracic artery (LITA)–to–left anterior descending coronary artery (LAD) graft as an established standard for coronary artery bypass,¹ cardiothoracic surgeons have been searching for other durable vascular conduits.² The use of the radial artery (RA) for coronary artery bypass graft surgery (CABG) was first introduced by Carpentier et al³ in 1973 but was abandoned due to an initially unfavorable outcome. Only in 1992 did Acar and colleagues reintroduce its use.⁴ In 1998, the same group reported excellent 5-year clinical and angiographic results.⁵ Since then, interest for using the RA has been renewed.

With the success of using the LITA, some have also looked at the right internal thoracic artery (RITA) as the secondary coronary conduit. According to the Society of Thoracic Surgeons database, the use of the RITA is, however, limited to just 4% of the CABG population.⁶ The underuse of the RITA is due to concerns regarding chest wall bleeding, sternal dehiscence, and infection, especially among diabetic patients, as well as extended operating time for harvesting.

Clinical studies have documented the superior long-term patency of the RA over the saphenous vein graft (SVG),⁷ a traditional conduit for the second and tertiary coronary territory. Some have pointed to the physiologic effect of the nitric oxide on the endothelium causing vascular relaxation in RA compared with the SVG.⁸ Whether the conventional open approach or the recently introduced endoscopic technique is used,⁹ the RA is easy to harvest. Concerns regarding RA spasm and patency have been dispelled with several studies showing excellent patency rates.^{10,11} With such excellent handling characteristics and patency findings, it is then necessary to delineate the long-term clinical impact of the RA.

In this study, we investigated the long-term patient survival after first-time isolated CABG with LITA-to-LAD graft and either RA or SVG as a secondary graft. We further performed subgroup analysis to delineate the effect of age, sex, and diabetes.

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Methods

Study Population

The study population consisted of consecutive patients who underwent CABG at Cedars-Sinai Medical Center in Los Angeles, California, between January 1, 1997, and December 31, 2001. All were isolated, non-redo CABG patients who received LITA-to-LAD as the primary coronary graft and a secondary graft using either RA (radial) or SVG (nonradial). SVG was also used for any additional bypass conduits. Postoperative follow-up duration was 12 years. The study was approved by the institutional review board.

Surgical Procedure and RA Harvesting

CABG was performed with cardiopulmonary bypass using both blood and crystalloid cardioplegia for arrest. Off-pump procedures were performed when the aorta was heavily diseased. Our primary indication in using the RA instead of the SVG was a surgeon choice. Patients with chronic renal disease on hemodialysis, Raynaud phenomenon, vasculitis, or equivocal ulnar artery collateral flow were excluded.

The collateral hand circulation was assessed using the Allen test and digital plethysmography before the operation. The nondominant extremity was generally selected as the harvest site. RA harvest was abandoned if the caliber of the vessel was <1 mm or there was significant calcification.

RA harvesting was performed via the conventional open forearm incision of about 20 cm. Gentle retraction of the brachioradialis muscle was done to enhance vessel exposure. Attention was given to avoid injury to the lateral antebrachial cutaneous nerve and the superficial branch of the radial nerve. Topical papaverine was injected into the RA after it was harvested. It was then stored in a saline-based solution until it was ready for anastomosis. Intravenous calcium channel blockers or nitroglycerin was started intraoperatively and continued postoperatively. Oral long-acting nitrates or calcium channel blockers were continued for up to 6 months postoperatively.

Clinical Data

Preoperative, operative, and postoperative characteristics were recorded. Patients were followed annually by use of mailed questionnaires, telephone interview, or physician office visit.

Clinical End Points

The primary end point was death from any cause, beginning at the time of operation through the last day of follow-up. All-cause mortality data were secured from our patient

follow-up and was supplemented by queries of the United States Social Security Death Index database to determine the timing of death.

Statistical Analysis and Propensity Patient Matching

Multivariable logistic regression (18 variables) was used to construct a propensity model for the propensity (probability) of receiving an RA graft. Continuous numerical predictors in the propensity model were age, ejection fraction, and body mass index. Binary predictors were sex, history of congestive heart failure, history of diabetes mellitus, history of hypertension, history of chronic obstructive pulmonary disease, history of cerebrovascular accident, history of peripheral vascular disease, history of angina, history of carotid endarterectomy, preoperative use of an intra-aortic balloon pump, prior percutaneous transluminal coronary angioplasty, use of thrombolysis, urgent/emergent (versus elective) status, and off-pump (versus on-pump) surgery. Two numerical predictors were the number of diseased coronary territory (reference=3 territories) and study year (reference=1996). These variables were incorporated in the propensity model by the use of indicator variables. Propensity matching to within ± 0.03 resulted in 260 matched pairs (520 subjects) for comparison.

Pairwise (RA versus SVG) comparisons of age, ejection fraction, and body mass index were made using the paired *t* test. The binary variables were compared using McNemar's test for related proportions. The number of diseased coronary territories was compared using the Wilcoxon signed rank test. Survival was estimated by the Kaplan–Meier method. To account for the clustering induced by the propensity matching, hazard ratios (HRs), robust standard errors, robust confidence intervals, and robust *P* values were calculated using the Cox proportional hazards model with a robust sandwich covariance matrix estimate to account for the intracluster dependence. A 2-sided 0.05 significance level was used throughout. Statistical calculations were made using SAS version 9.2 (SAS Institute).

Results

Patient Population

The study population consisted of 1248 consecutive patients with primary isolated CABG. The C-statistic for the propensity model was 0.86. Propensity-matching to within ± 0.03 resulted in 260 matched pairs (520 subjects) for comparison.

The baseline patient characteristics are shown in Table 1. Diabetes was documented in 192 patients (37%). Peripheral vascular disease and previous cerebrovascular accident were

Table 1. Propensity Matched-Pair Patients' Baseline Characteristics

Group	Radial Artery Group (n=260)	SVG Group (n=260)	P Value
Age, y	70.6±8.7	70.9±9.8	0.76
LVEF, %	53.6±13.5	53.3±15.6	0.78
BMI, kg/m ²	27.3±4.4	27.2±7.7	0.92
Male	181 (69.6)	183 (70.4)	0.92
CHF	39 (15.0)	42 (16.2)	0.82
DM	101 (38.8)	91 (33.5)	0.42
HTN	169 (65.0)	175 (67.3)	0.63
COPD	33 (12.7)	39 (15.0)	0.54
CVA	28 (10.8)	25 (9.6)	0.78
PVD	57 (21.9)	52 (20.0)	0.64
Angina	211 (81.2)	209 (80.4)	0.92
CEA	8 (3.1)	11 (4.2)	0.63
IABP	4 (1.5)	4 (1.5)	N/A
PTCA	61 (23.5)	51 (19.6)	0.35
Thrombolysis	5 (1.9)	5 (1.9)	N/A
Urgent/emergent	100 (38.5)	97 (37.3)	0.86
Off pump	43 (16.5)	47 (18.1)	0.73
Diseased coronary territory (1-3)	2.7±0.5	2.7±0.5	0.71

Values are mean±SD or n (%). SVG indicates saphenous vein graft; BMI, body mass index; CEA, carotid endarterectomy; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; N/A, not applicable; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease.

found in 109 (21%) and 53 (10%), respectively. Urgent or emergent CABG was performed in 197 (38%). No significant group differences were observed in the distribution of age, sex, presence of cardiovascular risk factors, or proportion of patients undergoing urgent surgery and off-pump procedure.

Previous myocardial infarction was noted in 78 and 87 of the RA and the SVG groups with statistical insignificance ($P=0.45$). The average number of bypass grafts between the 2 groups was also comparable ($P=0.40$) with 3.3 (SD=0.9) in the RA group and 3.2 (SD=0.8) in the SVG group. The RA was used primarily to graft the circumflex artery (201, 77%), the right coronary artery (39, 15%), and the diagonal (20, 8%).

Perioperative outcomes for the propensity-matched patients are noted in Table 2. The 30-day mortality rates were 3% and 1.5% for the RA and SVG groups, respectively. Perioperative myocardial infarction rates were 1% and 0% for the RA and SVG groups, and perioperative stroke rates were 2% and 3%, respectively. No sternal wound infections were noted in these matched patients. None of these differences were statistically significant.

Table 2. Perioperative Outcome for the Propensity Matched Patients

Outcome	Radial Artery Group (n=260)	SVG Group (n=260)	P Value
30-d mortality, n (%)	8 (3.1)	4 (1.5)	0.39
Perioperative MI, n (%)	3 (1.2)	0	0.25
Perioperative stroke, n (%)	5 (1.9)	7 (2.7)	0.77
Sternal wound infection, n (%)	0	0	N/A

MI indicates myocardial infarction; N/A, not applicable; SVG, saphenous vein graft.

The median follow-up in 520 patients was 9.4 years, and the interquartile range was 5.7 to 11.9 years. Follow-up in the RA subgroup (260 patients) was 10.3 years and the interquartile range was 5.7 to 11.9 years; follow-up in the SVG subgroup (260 patients) was 9.4 years and the interquartile range was 5.6 to 11.5 years. Follow-up was 99% complete; 1 patient in the RA group and 3 patients in the SVG group were lost to follow-up.

RA Versus SVG CABG Survival

Figure 1 shows the Kaplan–Meier curves for the propensity-matched patient survival. Early (1-year), mid-term (5-year), and long-term (12-year) survival rates in the RA group were 95±1.4%, 82±2.4%, and 52±1.4%, respectively, and those in the SVG group were 94±1.5%, 78±2.6%, and 43±3.3%. The estimated HR comparing the RA and SVG groups was 0.76 (95% CI=0.60 to 0.97, $P=0.03$).

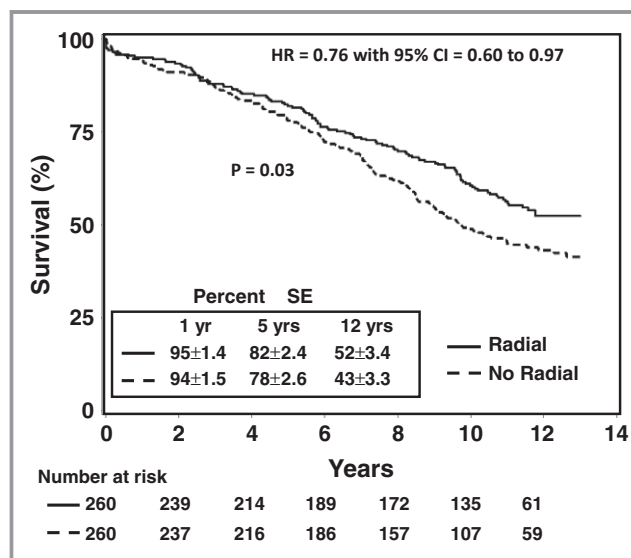


Figure 1. Kaplan–Meier overall propensity matched patient survival. HR indicates hazard ratio; SE, standard error.

RA Versus SVG CABG Survival (Sex Subgroup Analysis)

Early (1-year), mid-term (5-year), and long-term (12-year) survival rates in the male RA group were 97±1.4%, 86±2.7%, and 54±4.2%, respectively, and those in the male SVG group were 96±1.5%, 81±3.0%, and 48±4.1%. There was a trend toward improved RA survival in men (HR=0.84, 95% CI=0.61 to 1.15, P=0.26; Figure 2A).

Early (1-year), mid-term (5-year), and long-term (12-year) survival rates in women with RA were 91±1.4%, 75±4.9%, and 49±6.0%. Survival rates in women with SVG were 90±1.5%, 71±5.2%, and 31±5.8%, respectively. Over 12 years, there was a survival benefit between the use and nonuse of the RA (HR=0.62, 95% CI=0.41 to 0.94, P=0.024; Figure 2B).

RA Versus Non-RA CABG Survival (Age Subgroup Analysis)

Survival by age <65 years did not show a survival benefit between the RA versus SVG groups (HR=0.81, 95% CI=0.45 to 1.46, P=0.48; Figure 3A). Older patients (≥65 years of age) did show long-term (12-year) survival benefit between RA versus SVG groups: 48±4.0% versus 37±3.8% (HR=0.75, 95% CI=0.57 to 0.98, P=0.035; Figure 3B). Because of a smaller sample size, the age <65 group had lower statistical power (with HR=0.81) compared with the age >65 group (HR=0.75).

RA Versus SVG CABG Survival (Diabetes Status Subgroup Analysis)

The diabetic subgroup had the most significant survival benefit with the RA at both the 5 and 12 years (81±3.9% versus 73±4.7% and 48±5.4% versus 27±5.6%, respectively). The HR was 0.59 (95% CI=0.41 to 0.85, P=0.005; Figure 4A). The nondiabetic subgroup did not appear to be influenced by the use of RA (HR=0.86, 95% CI=0.62 to 1.81, P=0.35; Figure 4B).

Discussion

After Carpentier and coworkers reported the first use of the RA, its use was largely abandoned due to a high occlusion rate at 1-year follow-up secondary to intimal hyperplasia and vasospasm.¹² The higher occlusion rates were associated with trauma during harvest, such as mechanical dilation and external manipulation. The vasospastic response of the RA was greater than that of the internal thoracic artery because of a thicker media. Newer harvesting techniques and antispasmodic medications (ie, calcium channel blockers) were found to be effective in preventing postoperative vasoconstriction and increased long-term patency.

Today, the debate continues about the optimal secondary conduit for CABG after LITA-to-LAD grafts. Trends in multiple arterial grafting have led to renewed enthusiasm for the RA as a secondary CABG conduit, although the RITA has also

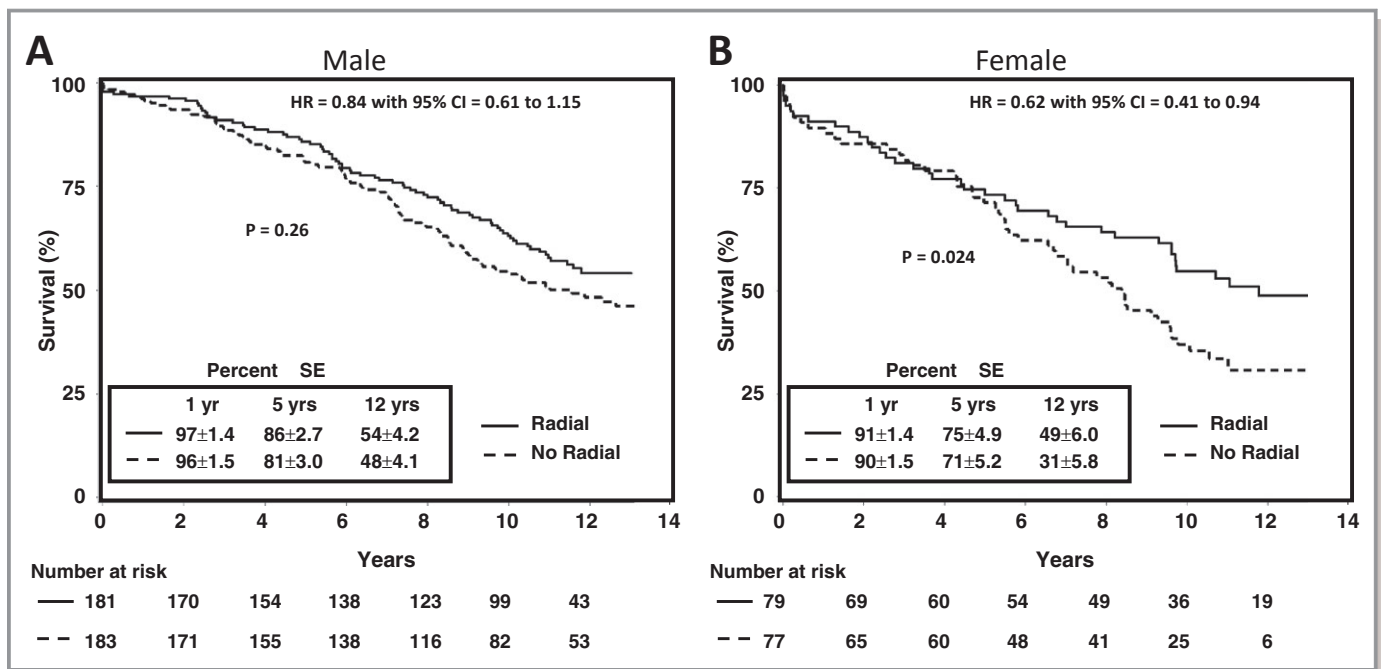


Figure 2. Kaplan–Meier estimate of patient survival by sex. HR indicates hazard ratio; SE, standard error.

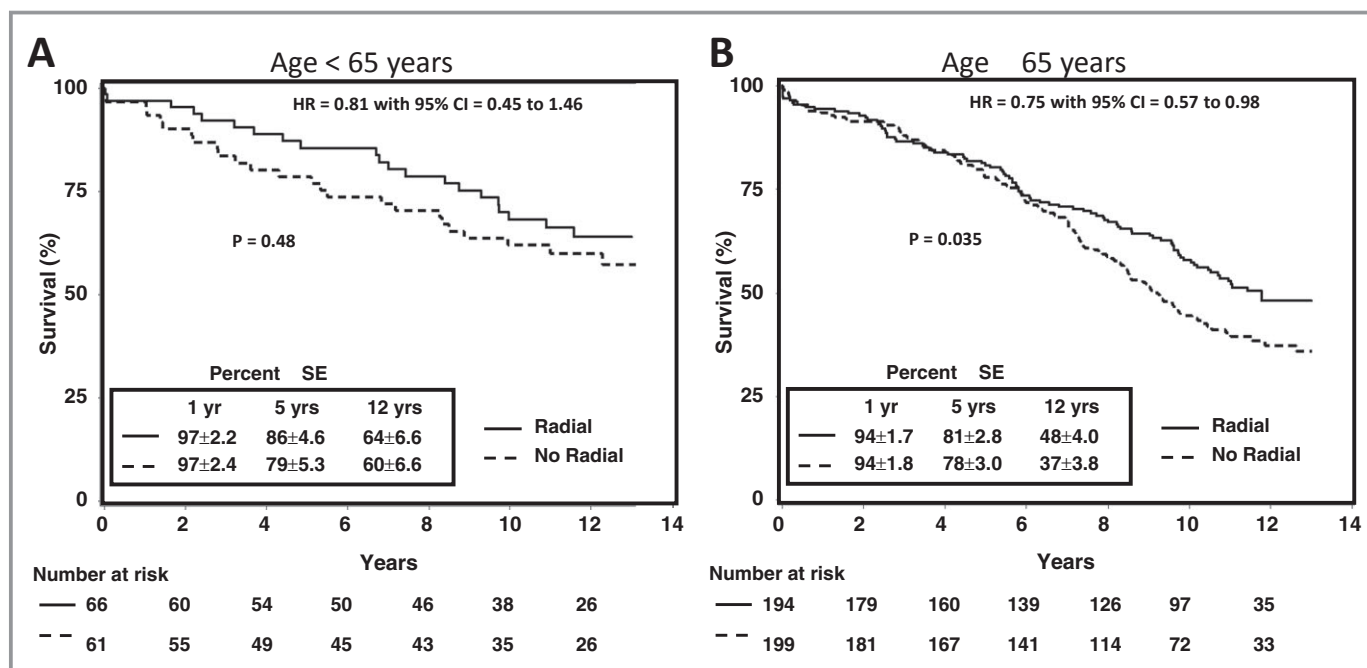


Figure 3. Kaplan–Meier estimate of patient survival by age group. HR indicates hazard ratio; SE, standard error.

garnered similar interest.^{13,14} The RA can be used as a free graft or a composite graft. It is an arterial graft with resistance to atherosclerosis. Its excellent handling versatility combined with the simultaneous harvesting of the LITA has led many groups to adopt the RA as the second conduit. Angiographic studies support the superior long-term patency of the RA compared with the SVG.^{15,16} Achouh and

colleagues in 2010 demonstrated excellent long-term RA patency (83%) in CABG up to 20 years postoperatively,¹⁰ but this was not significantly different compared with the RITA (87%) or SVG (81%).

There are several reports of the medium to longer-term clinical outcomes for RA grafting.¹⁷ Buxton and colleagues in 2003 reported a prospective randomized study comparing

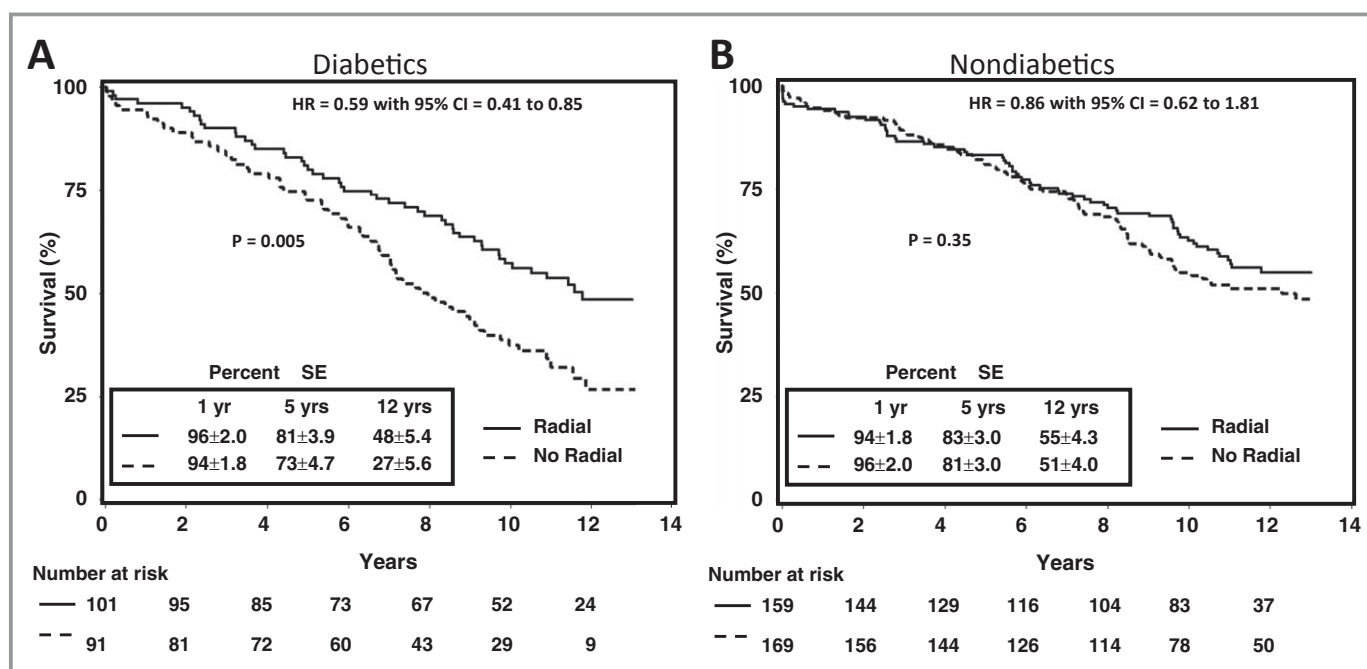


Figure 4. Kaplan–Meier estimate of patient survival by diabetic status. HR indicates hazard ratio; SE, standard error.

the RA with the free RITA and the SVG. Their 5-year interim results did not support the hypothesis of superior patency of the RA compared with the RITA or the SVG. The most recent update from the same group in 2010 continued to show no differences in patency rates with pending clinical results.¹⁸

Zacharias et al¹⁹ in 2004 evaluated the 6-year clinical outcomes of propensity-matched patients undergoing LITA-to-LAD grafting with either an additional RA graft or SVG as second conduit. In 925 propensity-matched patients, they found cumulative survival was better with the RA grafts. Angiographic data in restudied symptomatic patients showed a trend toward greater RA graft patency. They reported that the RA graft survival benefit remained when patients were subdivided on the basis of specific risk factors, with women, triple-vessel disease, younger patients (age ≤ 65 years), and diabetic patients having a more pronounced survival benefit. However, in their most recent update,²⁰ the 11-year Kaplan–Meier analysis showed essentially identical RA versus SVG survival for the diabetic patients.

Desai et al,²¹ in the 2007 Radial Artery Patency Study, examined randomized angiographic data in 440 RA versus 440 SVG grafts in CABG and showed RA was protective against occlusion, especially in women up to 12 months. A history of peripheral vascular disease was associated with higher risk of RA occlusion, while grafting to a vessel with proximal occlusion improved RA patency. The same group in 2008 showed, via angiographic data at 1-year post-CABG, that diabetes mellitus was an independent predictor of graft occlusion, although RA grafting was protective in this subgroup versus the SVG.²²

In light of these reports and conflicting results, we present a review of our long-term 12-year survival outcomes with the use of the RA in CABG. Overall, the benefits begin to appear at the mid-term 5-year mark, which correlates with the known time point when a notable percentage of saphenous vein occlusion begins. In the sex subgroup analysis, we observe a survival benefit in women with RA graft versus no RA graft. Although earlier studies have demonstrated protective effects of estrogen,²³ the Women's Health Initiative clinical study appeared to contradict this finding by showing increased risk for coronary artery disease with hormone replacement therapy.²⁴ More studies are required to elucidate the confounding metabolic and endocrine effects. Nevertheless, as observed in Figure 2, the female survival advantage with the RA shows a more rapid survival decline in the saphenous group compared with the men.

In the age subgroup analysis, we saw similar survival separation in those with age >65 years as in the women. Again, the effect appeared to correlate with the rapid survival decline in those in the SVG group beginning at 5 years. In the diabetic subgroup analysis, we also observed similar effects in

both the rate of survival decline and the timing of decline. Statistically, the effect of diabetes mellitus was the most prominent.

Diabetes mellitus is an established risk factor in CABG patients with an incidence between 20% and 49%. Diabetes increases the incidence of CAD and graft failure,²² but overall long-term survival is improved after CABG.²⁵ Most recently, the FREEDOM (Future REvascularization Evaluation in patients with Diabetes mellitus: optimal management of Multivessel disease) trial showed that diabetics with advanced coronary disease have reduced death rates and heart attack rates with CABG compared with percutaneous coronary intervention.²⁶ Diabetic patients have dysmetabolic syndrome, decreased endothelial nitric oxide production, increased inflammatory response (C-reactive protein, interleukin 6), altered platelet thrombogenesis, and increased premature graft failure.^{27,28} Because of the severity of the underlying coronary disease and the rapidity in atherosclerosis progression with the SVG, the RA graft provides the most significant benefit in diabetic subjects.

The main limitation of this study is its retrospective analysis. However, by applying a propensity-matched score, selection biases were minimized. Another limitation is the difficulty in obtaining angiographic examinations, and thus we were unable to correlate the patency and the status of the RA graft with clinical outcomes. Our age subgroup analysis based on age 65 had a smaller sample size for the younger population. Statistically, it was underpowered to show separation in survival between the RA and the SVG groups.

In summary, we have shown CABG using the RA in combination with the LITA-to-LAD group is associated with improved long-term overall survival ($P=0.03$). The long-term data allowed delineation of the clinical benefit beginning at 5 years postoperatively. Statistically, the benefit was most pronounced in the following order: diabetics ($P=0.005$), women ($P=0.02$), and the elderly ($P=0.04$). We believe that additional prospective randomized studies would validate our results and potentially expand the use of the RA for CABG in cardiac surgery.

Disclosures

None.

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