JAMA | Original Investigation

Association of Radial Artery Graft vs Saphenous Vein Graft With Long-term Cardiovascular Outcomes Among Patients Undergoing Coronary Artery Bypass Grafting

A Systematic Review and Meta-analysis

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IMPORTANCE Observational studies have suggested that the use of radial artery grafts for coronary artery bypass grafting may improve clinical outcomes compared with the use of saphenous vein grafts, but this has not been confirmed in randomized trials.

OBJECTIVE To compare clinical outcomes between patients receiving radial artery vs saphenous vein grafts for coronary artery bypass grafting after long-term follow-up.

DESIGN, SETTING, AND PARTICIPANTS Patient-level pooled analysis comparing radial artery vs saphenous vein graft in adult patients undergoing isolated coronary artery bypass grafting from 5 countries (Australia, Italy, Serbia, South Korea, and the United Kingdom), with enrollment from 1997 to 2009 and follow-up completed in 2019.

INTERVENTIONS Patients were randomized to undergo either radial artery (n = 534) or saphenous vein (n = 502) grafts for coronary artery bypass grafting.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of death, myocardial infarction, or repeat revascularization and the secondary outcome was a composite of death or myocardial infarction.

RESULTS A total of 1036 patients were randomized (mean age, 66.6 years in the radial artery group vs 67.1 years in the saphenous vein group; 376 [70.4%] men in the radial artery group vs 351 [69.9%] in the saphenous vein group); 942 (90.9%) of the originally randomized patients completed 10 years of follow-up (510 in the radial artery group). At a median (interquartile range) follow-up of 10 (10-11) years, the use of the radial artery, compared with the saphenous vein, in coronary artery bypass grafting was associated with a statistically significant reduction in the incidence of the composite outcome of death, myocardial infarction, or repeat revascularization (220 vs 237 total events; 41 vs 47 events per 1000 patient-years; hazard ratio, 0.73 [95% CI, 0.61-0.88]; $P < .001$) and of the composite of death or myocardial infarction (188 vs 193 total events; 35 vs 38 events per 1000 patient-years; hazard ratio, 0.77 [95% CI, 0.63-0.94]; $P = .01$).

CONCLUSIONS AND RELEVANCE In this individual participant data meta-analysis with a median follow-up of 10 years, among patients undergoing coronary artery bypass grafting, the use of the radial artery compared with the saphenous vein was associated with a lower risk of a composite of cardiovascular outcomes.

Editorial page 154

Supplemental content

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JAMA. 2020;324(2):179-187. doi:10.1001/jama.2020.8228

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The long-term clinical consequences of using the radial artery instead of the saphenous vein for coronary artery bypass grafting (CABG) remain uncertain. Observational studies have suggested that the use of the radial artery is associated with better postoperative outcomes,[1] but they are open to bias.[2]

The Radial Artery Database International Alliance, a pooled analysis of individual patient data from 5 randomized clinical trials (RCTs) comparing use of the radial artery and the saphenous vein for CABG, previously reported that the use of the radial artery was associated with a significantly lower incidence of the composite outcome of death, myocardial infarction, or repeat revascularization at 5-year follow-up.[3] No statistically significant difference in survival was found and the composite outcome was driven by repeat revascularization.

Due to the low number of events in the initial 5 years after surgery, the power of the 5-year analysis was limited. Because saphenous vein graft failure accelerates 5 years after surgery,[4] it might be anticipated that any potential clinical benefit of radial artery grafting would become more evident with a longer duration of follow-up.

In addition, because the majority of the trials included in the database mandated angiography over the first 5 years of follow-up, it is unclear to what extent the revascularization outcome may have been inflated due to incidental finding of asymptomatic graft failure. After 5 years, all but 1 of the trials did not mandate imaging control, and extension of follow-up is necessary to elucidate the effect of per-protocol angiography on the outcomes.

The objective of the current study was to compare long-term clinical outcomes between patients undergoing radial artery vs saphenous vein grafts for CABG, based on 10 years of follow-up.

Key Points

Question Is the use of the radial artery instead of the saphenous vein for coronary artery bypass surgery associated with a lower risk of adverse cardiac events in the long term?

Findings In this individual participant data meta-analysis from 5 randomized clinical trials that included 1036 patients undergoing coronary artery bypass grafting, randomization to receive radial artery compared with saphenous vein graft was associated with an incidence of a composite of death, myocardial infarction, or repeat revascularization of 41 vs 47 events per 1000 person-years after a median follow-up of 10 years, a difference that was statistically significant.

Meaning Over 10 years of follow-up, radial artery graft compared with saphenous vein graft was associated with a lower risk of a composite of cardiovascular outcomes.

Methods

Project

Ethics approval and oral participant consent for the study was obtained locally by each study team. The Weill Cornell Medicine Institutional Review Board waived the need for ethics approval for the pooled analysis.

Study Protocol

The protocol for the present analysis was published a priori, and the analytic plan and the outcomes were defined before the start of the analysis.[5]

Selection of the Trials

A systematic literature search was performed to identify RCTs that compared use of the radial artery and the saphenous vein in patients who underwent CABG. MEDLINE and Embase were searched in January 2019, and the search was updated in March 2020. The following keywords were combined with the Boolean operator *or*: *radial artery*, *saphenous vein*, and *coronary artery bypass grafting*. Study inclusion was assessed independently by 2 investigators (A.D. and I.H.). Disagreements were discussed and resolved by consensus. In addition, the bibliographies of all studies were searched to identify additional publications. Details of the search strategy are provided in the Supplement.[3] The PRISMA flowchart[6] and the Cochrane Collaboration's tool for assessing the risk of bias for the included RCTs are provided in eFigures 1 and 2 in the Supplement.

Follow-up

Clinical follow-up to 10 years or to the maximal possible follow-up for each patient was requested from the individual trial teams. Follow-up was performed by telephone interview for the study by Nasso et al,[7] the Radial Artery Patency and Clinical Outcome (RAPCO) trial,[8] and the study by Petrovic et al.[9] For the Radial Artery vs Saphenous Vein Patency (RSVP) trial,[10] follow-up data were obtained from the Royal Brompton & Harefield NHS Foundation Trust electronic patient record database and from questionnaires sent to general practitioners. For the Song et al[11] trial, the Statistic Korea database as well as telephone interviews were used to obtain follow-up data. No central verification of data sources was performed. In the Song et al,[11] Petrovic et al,[9] and RSVP[10] trials, the assessors of the clinical outcomes were blinded to the treatment assignment. For the Nasso et al[7] and RAPCO[8] trials, no formal blinding protocol was adopted, but assessors were not involved in the study.

Data Collection and Merging

An electronic preformatted data collection form containing core minimum data requirements was sent to each trial team. De-identified data were received by the coordinating center at Weill Cornell Medicine and checked for quality, completion, and consistency with both the 5-year analysis and previous publications. Discrepancies were resolved through direct consultation with the individual trial teams. Data elements were then consolidated into a master database. All variable definitions were similar to those used in the 5-year analysis.[3]

Outcomes

The primary outcome was a composite of major adverse cardiac events defined as death from any cause, myocardial infarction, or repeat revascularization. The secondary outcome

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was a composite of death from any cause or myocardial infarction. For all the events, individual trial definitions were used. Each component of the composite outcomes was analyzed separately but not formally tested, with the exception of mortality, which was tested as a post hoc exploratory outcome. Prespecified subgroup analyses were performed by age, sex, diabetes status, preoperative history of myocardial infarction, left ventricular ejection fraction, preoperative kidney function, and radial artery target vessel.

Statistical Analysis

Baseline and intraoperative characteristics in the 2 groups were reported as numbers and percentages for categorical variables and as means and SDs or medians and interquartile ranges for continuous variables. Parametric or nonparametric tests were used to compare the 2 groups, as appropriate. A comparison of baseline characteristics between patients who were lost to follow-up and those included in the analysis was performed to ensure that patients with follow-up data were representative of the parent cohorts.

Outcomes were reported as frequencies, cumulative incidence, and linearized event rates per 1000 patient-years to account for different follow-up duration across individual trials. The cumulative incidence of nonfatal events was determined with death as a competing risk. In the primary analysis, patients were analyzed according to their randomization group.

Association between treatment and outcomes were estimated using a mixed-effect Cox regression model, with treatment allocation included as fixed effect and trial identifiers included as random effect. Treatment effects were presented as hazard ratios (HRs) and 95% CIs. The proportional hazards assumption was verified using Schoenfeld residuals. For nonfatal events, competing risks regression analysis was based on the Fine and Gray proportional subhazards model.

The following effect modifiers on the primary end point were tested using subgroup analysis: age, sex, diabetes status, prior myocardial infarction, left ventricular ejection fraction less than 50%, kidney insufficiency,[12] and radial artery target vessel. The results were displayed as a forest plot.

Multiple sensitivity analyses were performed. To investigate the effect of protocol-mandated angiography on the difference in the outcomes between the groups, separate analyses of repeat revascularization and death and of the primary and secondary composite end points were performed for the period before and after the fifth year of follow-up. Association between treatment and the primary outcome was reestimated according to the conduit received.

The primary analysis was repeated using a 2-stage approach where a β coefficient with a relative standard error for the association between treatment and outcomes was obtained for each individual trial using a Cox regression model. Estimates of the association between treatment and outcomes across individual trials were then pooled in a second step using the generic inverse variance method with a random-effect model. Trial-level and pooled estimates were reported as HRs and 95% CIs; risk distribution was presented using forest plots with weighting according to a random-effect model. Heterogeneity across trials was assessed using I^2 statistics. I^2 values less than 25% defined low heterogeneity; 25% to 50%, moderate heterogeneity; and greater than 50%, high heterogeneity. Leave-1-out analysis was used to assess the influence of individual trials on the final estimate.

To account for potential confounders and postrandomization imbalance between groups, the analysis for the primary end point and for mortality was repeated using a fully adjusted mixed-effect Cox model. To account for the loss to follow-up, 2 sensitivity analyses were performed for the primary outcome. In the first analysis, drop-outs were treated as nonevents and assigned 10 years follow-up in both groups. In the second analysis, varying scenarios for the event rate in each group of patients lost to follow-up were calculated, to the extreme case in which all patients lost to follow-up in the saphenous vein group were considered nonevents and assigned 10 years follow-up and all patients lost to follow-up in the radial artery group were considered dead at 10 years of follow-up (tipping point analysis). In addition, an analysis limited only to the studies at lowest risk of bias based on the Cochrane Collaboration's tool for assessing risk of bias was performed.

The saphenous vein group was used as the reference in all analyses. A fixed-order sequential testing method was used with the primary outcome tested first at an α level of .05 and the secondary outcome tested at the same level if the primary outcome was statistically significant. All *P* values were 2-sided, and *P* values less than .05 were deemed statistically significant. No significance testing was done for subgroup analyses or for the individual components of the composite outcomes, except mortality. For these analyses, only estimates of the association between treatment and outcomes and corresponding 95% CIs were provided. Because of the lack of adjustment for multiple comparisons and the potential for type I error, the results of the secondary, subgroup, and post hoc analyses should be interpreted as exploratory. Statistical analyses were performed using R, version 3.6.1, and the following packages: coxme, meta, prodlim, Publish, and riskRegression.

Results

Study Population

A total of 774 studies were identified from the literature search, and 38 were included for full-text review. Five trials met the inclusion criteria.[7-11] The principal investigators of all the trials were contacted and all agreed to extend the follow-up and share the data.

Two of the included trials (Nasso et al[7] and RAPCO[8]) compared CABG with the radial artery vs either the saphenous vein or the right internal thoracic artery in separate comparisons. For those trials, only the radial artery and saphenous vein groups were included. Details of the individual trials are provided in **Table 1**.[7-11]

Overall, 1036 patients (534 patients randomized to the radial artery group and 502 to saphenous vein group) were included. Baseline characteristics of the patients are summarized in **Table 2**. There were no statistically significant differences in any of the explored variables between the groups.

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Table 1. Details of the Trials Included in a Study of the Association of Radial Artery vs Saphenous Vein Graft With Cardiovascular Outcomes Among Patients Undergoing Coronary Artery Bypass Grafting

Characteristic	Petrovic et al[9]	RAPCO[8]	RSVP[10]	Nasso et al[7]	Song et al[11]
Study period (enrollment)	2001-2003	1997-2004	1998-2000	2003-2006	2008-2009
Country of origin	Serbia	Australia	United Kingdom	Italy	South Korea
Institution	Belgrade University School of Medicine, Belgrade, Serbia	University of Melbourne, Victoria, Australia	Royal Brompton Hospital, London, United Kingdom	Italy (multicenter)	Yonsei University Health System, Seoul, South Korea
No. of patients	200	225	142	409	60
Radial artery group	100	113	82	204	35
Saphenous vein group	100	112	60	205	25
Age, mean (SD), y					
Radial artery group	56.3 (6.1)	72.9 (62.3-83.5)	58.0 (6.0)	70.5 (3.1)	72.7 (3.2)
Saphenous vein group	57.1 (6.5)	73.2 (64.0-82.4)	59.0 (7.0)	69.7 (3.5)	74.6 (3.8)
Men, No. (%)					
Radial artery group	73 (73)	91 (81)	79 (96)	117 (57)	17 (49)
Saphenous vein group	73 (73)	91 (81)	58 (97)	121 (59)	14 (56)
Women, No. (%)					
Radial artery group	27 (27)	22 (19)	3 (4)	87 (43)	18 (51)
Saphenous vein group	27 (27)	21 (19)	2 (3)	84 (41)	11 (44)
LVEF	Mean (SD), %	All patients had LVEF >35% (per inclusion criteria)	All patients had LVEF ≥25% (per inclusion criteria)	Patients with LVEF <30%, %	Patients with LVEF <35%, %
Radial artery group	48.8 (10.7)			14.8	10.0
Saphenous vein group	48.0 (10.8)			13.9	13.0
Chronic pulmonary disease, No. (%)					
Radial artery group	9 (9)	NR	NR	57 (28.2)	NR
Saphenous vein group	8 (8)	NR	NR	56 (27.7)	NR
Diabetes, No. (%)					
Radial artery group	39 (39)	50 (44)	15 (18)	73 (36)	15 (43)
Saphenous vein group	43 (43)	52 (46)	10 (17)	77 (38)	13 (52)
Radial artery target vessel stenosis, %	>80	>70	>70	>70	NR
Radial artery grafts to the circumflex coronary artery, %	83	100	100	47	98
Crossover rate, %					
Radial artery group	0	5.3	0	3.4	0
Saphenous vein group	0	1.8	0	4.9	0
CPB details	NR	All on pump	All on pump	All on pump	All off pump
Details of postoperative medical therapy	Any CCB for 1 y, statins, β blockers, and aspirin	Amlodipine for 6 mo and aspirin	Diltiazem for 6 wk and aspirin	Diltiazem for 6 mo, statins, and aspirin	Diltiazem indefinitely, statins, β blockers, and aspirin

Abbreviations: CCB, chronic calcium channel blocker therapy; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; NR, not reported; RAPCO, Radial Artery Patency and Clinical Outcome Trial; RSVP, Radial Artery vs Saphenous Vein Patency Study.

The radial artery and saphenous vein groups were similar in terms of demographics (mean age, 66.6 vs 67.1 years; 70.4% vs 69.9% men), cardiovascular risk factors (33.9% vs 35.3% patients with diabetes), left ventricular ejection fraction, target vessel distribution, and number of grafts received. There was no significant difference in baseline characteristics between

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Table 2. Baseline Characteristics of Patients in a Study of the Association of Radial Artery vs Saphenous Vein Graft With Cardiovascular Outcomes Among Patients Undergoing Coronary Artery Bypass Grafting

Characteristic	No. (%)		Absolute difference (95% CI)
	Radial artery group (n = 534)	Saphenous vein group (n = 502)	
Age, mean (SD), y	66.6 (9.3)	67.1 (9.8)	0 (−1.16 to 1.16)
Men	376 (70.4)	351 (69.9)	0.49 (-5.06 to 6.06)
Women	158 (29.6)	151 (30.1)	0.40 (-3.90 to 4.48)
Diabetes	181 (33.9)	177 (35.3)	1.36 (-4.41 to 7.14)
Prior myocardial infarction	164 (30.7)	160 (31.9)	1.16 (-4.47 to 6.80)
Elective admission	469 (87.8)	456 (90.8)	3.01 (-0.78 to 6.78)
Kidney insufficiency[a]	45 (8.4)	46 (9.2)	0.36 (-3.77 to 4.45)
Left ventricular ejection fraction <50%	70 (13.1)	64 (12.7)	0.36 (-3.77 to 4.45)
Target vessel			4.21 (-1.02 to 9.43)
Left circumflex coronary artery	415 (77.7)	369 (73.5)	
Right coronary artery	119 (22.3)	133 (26.5)	
No. of grafts, mean (SD)	3.1 (0.7)	3.1 (0.6)	0 (−8.00 to 8.00)
Proximal anastomosis site			2.85 (-0.29 to 6.00)
Ascending aorta	489 (91.5)	474 (94.4)	
Internal thoracic artery	45 (8.5)	28 (5.6)	

[a] Kidney insufficiency was defined as preoperative serum creatinine greater than 1.5 mg/dL.[12]

Table 3. Main Outcomes in a Study of the Association of Radial Artery vs Saphenous Vein Graft With Cardiovascular Outcomes Among Patients Undergoing Coronary Artery Bypass Grafting

Outcome	Radial artery group (n = 534)				Saphenous vein group (n = 502)				Treatment effect[a]	
	Events, No. (%)	Events per 1000 patient-years	Cumulative incidence at 10 y (95% CI)	Cumulative incidence at 15 y (95% CI)	Events, No. (%)	Events per 1000 patient-years	Cumulative incidence at 10 y (95% CI)	Cumulative incidence at 15 y (95% CI)	Hazard ratio (95% CI)	*P* value
Death, myocardial infarction, or repeat revascularization	220 (41.2)	41	31.0 (27.0-34.9)	52.5 (46.1-58.9)	237 (47.2)	47	41.6 (37.2-46.0)	61.5 (54.5-68.6)	0.73 (0.61-0.88)	<.001
Death or myocardial infarction	188 (35.2)	35	25.4 (21.6-29.1)	47.8 (41.2-54.5)	193 (38.4)	38	33.0 (28.8-37.3)	57.1 (49.5-64.7)	0.77 (0.63-0.94)	.01

[a] Results from mixed-effect Cox regression model with individual trials included as a random effect (saphenous vein graft group is the reference group).

patients lost to follow-up and those included in the analysis (eTable 1 in the Supplement).

The median (interquartile range) follow-up was 10 (10-11) years in both groups; 942 of 1036 patients (90.9%) had a follow-up of at least 10 years (details on patients lost to follow-up are reported in eFigure 3 in the Supplement). All patients with follow-up data had information available for each of the included outcomes. The proportional hazards assumption was met for all of the explored outcomes (eFigure 4 in the Supplement).

Risk of Bias

The risk of bias in the included trials was rated as low to moderate (eFigure 2 in the Supplement).

Main Outcomes

The main outcomes are reported in **Table 3**. The use of the radial artery for CABG, compared with the saphenous vein, was associated with a significantly lower incidence of the composite primary end point of death, myocardial infarction, or repeat revascularization (220 vs 237 events; 41 vs 47 events per 1000 patient-years; HR, 0.73 [95% CI, 0.61-0.88]; $P < .001$; **Figure 1**A). The use of the radial artery was associated with a significantly lower incidence of the composite secondary end point of death or myocardial infarction compared with the saphenous vein (188 vs 193 events; 35 vs 38 events per 1000 patient-years; HR, 0.77 [95% CI, 0.63-0.94]; $P = .01$; Figure 1B). In a post hoc analysis, the use of the radial artery was also associated with a significantly lower incidence of death (128 vs 134 events; 24 vs 27 events per 1000 patient-years; HR, 0.73 [95% CI, 0.57-0.93]; $P = .01$; **Table 4** and eFigure 5 in the Supplement).

The incidence of myocardial infarction was 72 events in the radial artery group and 81 events in the saphenous vein group (13 vs 16 events per 1000 patient-years; HR, 0.74 [95% CI, 0.54-1.02]). The incidence of repeat revascularization was 63 events in the radial artery group and 86 events in the saphenous vein group (12 vs 17 events per 1000 patient-years; HR, 0.62 [95% CI, 0.45-0.86]) (Table 4 and eFigure 5 in the Supplement).

The HR for the primary outcome was similar during and after the first 5 years of follow-up (0.71 [95% CI, 0.52-0.95]

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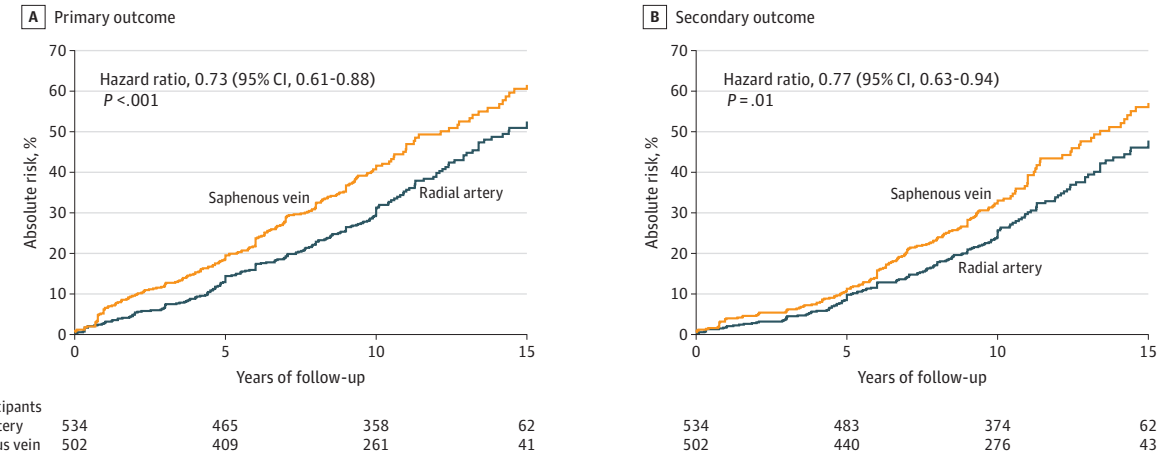
Figure 1. Cumulative Incidence of Primary and Secondary Composite Outcomes in a Study of the Association of Radial Artery vs Saphenous Vein Graft With Cardiovascular Outcomes Among Patients Undergoing Coronary Artery Bypass Grafting



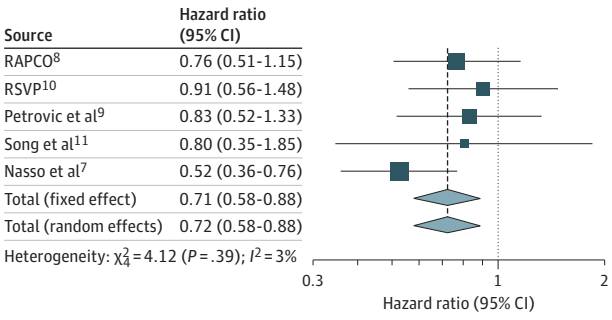
A, Cumulative incidence of the composite outcome of death, myocardial infarction, or repeat revascularization. Median (interquartile range) observation time: 10.0 (8.5-11.4) years in the radial artery group vs 10.0 (6.1-10.2) years in the saphenous vein group. B, Cumulative incidence of the outcome of death or myocardial infarction. Median (interquartile range) observation time: 10.0 (9.2-12.1) years in the radial artery group vs 10.0 (7.0-10.4) years in the saphenous vein group (patients analyzed according to their randomization group).

Table 4. Post Hoc Outcomes in a Study of the Association of Radial Artery vs Saphenous Vein Graft With Cardiovascular Outcomes Among Patients Undergoing Coronary Artery Bypass Grafting

	Radial artery group (n = 534)				Saphenous vein group (n = 502)				Treatment effect[a]	
Outcome	Events, No. (%)	Events per 1000 patient-years	Cumulative incidence at 10 y (95% CI)	Cumulative incidence at 15 y (95% CI)	Events, No. (%)	Events per 1000 patient-years	Cumulative incidence at 10 y (95% CI)	Cumulative incidence at 15 y (95% CI)	Hazard ratio (95% CI)	*P* value
Death	128 (24.0)	24	14.0 (11.1-17.0)	34.6 (28.2-41.0)	134 (26.7)	27	19.8 (16.2-23.4)	47.1 (38.9-55.3)	0.73 (0.57-0.93)	.01
Myocardial infarction	72 (13.5)	13	12.0 (9.2-14.7)	15.2 (11.6-18.7)	81 (16.1)	16	15.6 (12.3-18.8)	19.3 (14.8-23.8)	0.74 (0.54-1.02)	
Repeat revascularization	63 (11.8)	12	11.3 (8.6-14.0)	11.8 (8.9-14.6)	86 (17.1)	17	16.4 (13.2-19.7)	18.2 (14.4-22.0)	0.62 (0.45-0.86)	

[a] Results from mixed-effect Cox regression model with individual trials included as a random effect (saphenous vein graft group is the reference group).

Figure 2. Forest Plot of the Meta-analytic Estimate for the Composite Primary End Point of Death, Myocardial Infarction, or Revascularization in a Study of the Association of Radial Artery vs Saphenous Vein Graft With Cardiovascular Outcomes Among Patients Undergoing Coronary Artery Bypass Grafting



vs 0.75 [95% CI, 0.59-0.94]; eFigure 6 in the Supplement). The analysis of outcomes in the first 5 years of follow-up and after the fifth year of follow-up is provided in eFigures 6 to 9 in the Supplement.

The results of the analysis based on the conduit used were consistent with the main analysis (eFigure 10 in the Supplement). The results of the 2-stage analysis for the primary end point were consistent with the main analysis (HR, 0.72 [95% CI, 0.58-0.88]; **Figure 2** and eFigure 11 in the Supplement), with no statistically significant heterogeneity across trials (I^2 = 3%). The adjusted HR for the primary outcome (0.73 [95% CI, 0.61-0.88]) was similar to the unadjusted HR.

The results of the sensitivity analyses to account for the loss to follow-up were consistent with the main analysis (eTable 2 and eFigures 12-13 in the Supplement). In particular, when all patients lost to follow-up in the saphenous vein group were considered as nonevents and assigned 10 years follow-up and all patients lost to follow-up in the radial artery group were considered dead at 10 years of follow-up, the HR for the primary outcome was 0.81 (95% CI, 0.68-0.97) (eFigure 14 in the Supplement).

The event rates by trial are shown in eFigure 15 and eTables 3 to 5 in the Supplement. Results of an analysis limited only to the studies at the lowest risk of bias (RSVP and RAPCO) were consistent with the main analysis (HR, 0.79 [95%

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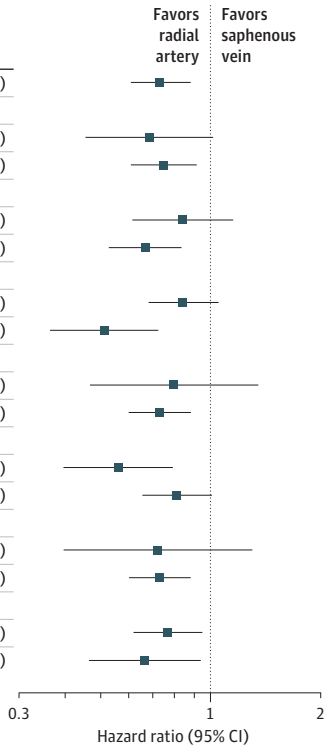
Figure 3. Subgroup Analysis for the Primary Composite Outcome in a Study of the Association of Radial Artery vs Saphenous Vein Graft With Cardiovascular Outcomes Among Patients Undergoing Coronary Artery Bypass Grafting

	No. of patients/total No. (%)		
	Radial artery group	Saphenous vein group	Hazard ratio (95% CI)
Overall	220/534 (41)	237/502 (47)	0.73 (0.61–0.88)
Aged 75 y or older			
Yes	43/80 (47)	56/92 (51)	0.68 (0.45–1.02)
No	177/454 (40)	181/410 (44)	0.74 (0.61–0.92)
Diabetes			
Yes	87/181 (48)	94/177 (53)	0.84 (0.61–1.15)
No	133/353 (37)	143/325 (44)	0.66 (0.53–0.83)
Sex			
Men	162/376 (43)	156/351 (44)	0.84 (0.68–1.05)
Women	58/158 (37)	81/151 (54)	0.51 (0.36–0.72)
LVEF <50%			
Yes	26/70 (37)	29/64 (45)	0.80 (0.47–1.35)
No	194/464 (42)	208/438 (47)	0.73 (0.60–0.88)
Prior myocardial infarction			
Yes	56/164 (34)	79/160 (49)	0.56 (0.40–0.79)
No	164/370 (44)	158/342 (46)	0.81 (0.65–1.01)
Kidney insufficiency			
Yes	23/45 (51)	24/46 (52)	0.72 (0.40–1.30)
No	197/489 (40)	213/456 (47)	0.73 (0.60–0.88)
Target vessel			
Left coronary artery	164/415 (39)	164/369 (44)	0.76 (0.62–0.95)
Right coronary artery	56/119 (57)	73/133 (55)	0.66 (0.46–0.94)



Subgroup analysis for the primary composite outcome of death, myocardial infarction, or repeat revascularization. Kidney insufficiency was defined as preoperative serum creatinine greater than 1.5 mg/dL.[12] LVEF indicates left ventricular ejection fraction.

CI, 0.58-1.09] for the primary outcome; eFigure 2 in the Supplement). Results of subgroup analyses are shown in **Figure 3**.

Discussion

In this patient-level analysis of 5 RCTs including a total of 1036 patients with a median follow-up of 10 years, the use of the radial artery for CABG was associated with a statistically significant lower incidence of the composite outcomes of death, myocardial infarction, or repeat revascularization and of death or myocardial infarction compared with the use of the saphenous vein.

Observational studies have found that postoperative survival is longer when the radial artery is used as a second conduit for CABG compared with the saphenous vein.[1] A meta-analysis of 14 adjusted observational comparative series (20 931 patients) found that at a mean follow-up of 6.6 years, mortality was 24.5% in the radial artery group vs 34.2% in the saphenous vein group (incidence rate ratio, 0.74 [95% CI, 0.63-0.87]).[1] However, observational comparative CABG studies are susceptible to treatment allocation and confounding bias, which could account for the reported difference.[2]

Previous randomized comparisons between use of the radial artery and the saphenous vein for CABG were underpowered to detect statistically significant differences in clinical outcomes, and even the previous report from this database at 5-year follow-up had limited power.[3] In addition, in the 5-year analysis, the use of per-protocol angiography by the majority of the trials mandated caution in the interpretation of the reported differences.

The only large RCT on the use of single vs multiple arterial grafts for CABG is the Arterial Revascularization Trial (ART),[13] which compared single and bilateral internal mammary artery grafting in 3102 patients. In ART,[13] there was no statistically significant difference in survival (HR, 0.96 [95% CI, 0.82-1.12]) or event-free survival (HR, 0.90 [95% CI, 0.79-1.03]) at 10 years.

The results of ART differ from the results of the present analysis, in which a lower risk of cardiac events at the 10-year follow-up was found in patients in the radial artery group compared with the saphenous vein group. A significant reduction in the incidence of death was also found in the radial artery group, but this was a post hoc analysis and the results must be considered hypothesis-generating.

One of the potential explanations for the discrepant results between ART and the current study is that the crossover rate from the bilateral to single arterial group in ART was relatively high (13.9%). Crossover, especially from the experimental to the control group, is known to dilute the treatment effect.[14] In the present study, the crossover rate was low (2.4%) and it is possible that better deliverability of the intervention, and not biologic differences between the radial artery and the internal thoracic artery, explains the difference between the 2 analyses. The use of bilateral internal thoracic arteries is technically more complex than the use of the radial artery and it

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has been shown that experience of the surgeon plays a key role in the former, but not the latter, procedure.[15] In addition, the use of the radial artery in 21.8% of the patients assigned to the control group in ART may have further diluted the association between treatment and outcomes and contributed to the null results.

Currently, the Randomized Comparison of the Outcome of Single vs Multiple Arterial Grafts (ROMA) trial (ClinicalTrials.gov 1703018094) is testing the multiple arterial graft hypothesis, including an effect on mortality, in a sample of 4300 patients.[16] In ROMA, the second arterial graft can be either the radial artery or an internal thoracic artery, and the results are expected after 2025.

Limitations

This study has several limitations. First, there was a lack of standardized outcomes definitions, a central adjudicating committee, and data source verification. Second, the surgical procedures were performed more than a decade ago and the operative and postoperative protocols may not reflect the current practice. Third, the trials were performed in different countries and there were differences in surgical techniques and postoperative protocols. Fourth, the trials had different sample sizes and contributed differently to the result of the pooled analysis, with larger trials having a larger contribution to the final estimate. However, there was no heterogeneity in the association between treatment and outcomes among the trials, and the results remained robust in the sensitivity analyses. Fifth, the number of patients lost to follow-up was higher in the saphenous vein group, and this may have introduced bias. However, results of the sensitivity analyses performed to account for the loss to follow-up were consistent with those of the main analysis. Sixth, the number of patients included is relatively limited and, even at 10 years follow-up, the analysis may be underpowered for some comparisons.

Conclusions

In this individual participant data meta-analysis with a median follow-up of 10 years, among patients undergoing CABG, the use of the radial artery compared with saphenous vein graft was associated with a lower risk of a composite of cardiovascular outcomes.

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Accepted for Publication: May 1, 2020.

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Obtained funding: Gaudino, Moat.
Administrative, technical, or material support: Gaudino, Biondi-Zoccai, Raman, Buxton, Collins, Petrovic, Yoo, Di Franco, Moscarelli, Girardi.
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Conflict of Interest Disclosures: Dr Fremes reported receiving grants from the University of Toronto during the conduct of the study and grants from the Canadian Institutes of Health Research outside the submitted work. Dr Biondi-Zoccai reported consulting for Abbott Vascular and Bayer. Dr Moat reported being an employee of Abbott, Santa Clara. Dr Puskas reported receiving royalties from surgical instruments invented by the author from Scanlan Inc and personal fees from Medtronic outside the submitted work and having a patent to surgical instruments issued and licensed, with royalties paid. Dr Hare reported receiving personal fees from the National Health and Medical Research Council of Australia and grants from the National Heart Foundation of Australia during the conduct of the study and personal fees from Amgen, AstraZeneca, Merck, and Pfizer and nonfinancial support from Lundbeck, Servier, and Vifor outside the submitted work. No other disclosures were reported.

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Funding/Support: This project was funded by the Department of Cardiothoracic Surgery of Weill Cornell Medicine in New York. Dr Fremes was supported in part by the Bernard S. Goldman Chair in Cardiovascular Surgery. Dr Benedetto was supported by the Bristol Biomedical Research Centre.

Role of the Funder/Sponsors: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Data Sharing Statement: The data, analytic methods, and study materials will be made available to other researchers upon reasonable request and approval by the steering committee. Data will be provided by the first author.

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