ORIGINAL ARTICLE

Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery

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ABSTRACT

BACKGROUND

The use of radial-artery grafts for coronary-artery bypass grafting (CABG) may result in better postoperative outcomes than the use of saphenous-vein grafts. However, randomized, controlled trials comparing radial-artery grafts and saphenous-vein grafts have been individually underpowered to detect differences in clinical outcomes. We performed a patient-level combined analysis of randomized, controlled trials to compare radial-artery grafts and saphenous-vein grafts for CABG.

METHODS

Six trials were identified. The primary outcome was a composite of death, myocardial infarction, or repeat revascularization. The secondary outcome was graft patency on follow-up angiography. Mixed-effects Cox regression models were used to estimate the treatment effect on the outcomes.

RESULTS

A total of 1036 patients were included in the analysis (534 patients with radial-artery grafts and 502 patients with saphenous-vein grafts). After a mean (±SD) follow-up time of 60±30 months, the incidence of adverse cardiac events was significantly lower in association with radial-artery grafts than with saphenous-vein grafts (hazard ratio, 0.67; 95% confidence interval [CI], 0.49 to 0.90; P=0.01). At follow-up angiography (mean follow-up, 50±30 months), the use of radial-artery grafts was also associated with a significantly lower risk of occlusion (hazard ratio, 0.44; 95% CI, 0.28 to 0.70; P<0.001). As compared with the use of saphenous-vein grafts, the use of radial-artery grafts was associated with a nominally lower incidence of myocardial infarction (hazard ratio, 0.72; 95% CI, 0.53 to 0.99; P=0.04) and a lower incidence of repeat revascularization (hazard ratio, 0.50; 95% CI, 0.40 to 0.63; P<0.001) but not a lower incidence of death from any cause (hazard ratio, 0.90; 95% CI, 0.59 to 1.41; P=0.68).

CONCLUSIONS

As compared with the use of saphenous-vein grafts, the use of radial-artery grafts for CABG resulted in a lower rate of adverse cardiac events and a higher rate of patency at 5 years of follow-up. (Funded by Weill Cornell Medicine and others.)

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*A complete list of the RADIAL investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Despite the recommendations of the current guidelines, the use of multiple arterial grafts for coronary-artery bypass grafting (CABG) has not been widely adopted by the surgical community, and the great majority of patients in North America and Europe currently receive saphenous-vein grafts in addition to an internal-thoracic-artery graft to the left anterior descending coronary artery.[1] Resistance among surgeons to the use of multiple arterial grafts can be explained, at least in part, by the fact that the clinical benefit of additional arterial grafts that has been reported in observational studies has not been confirmed in randomized clinical trials.[2] Although several trials have shown higher rates of angiographic patency in association with radial-artery grafts than with saphenous-vein grafts,[2] these trials were individually underpowered to detect differences in the frequency of clinical events. Therefore, whether the use of radial-artery grafts can improve clinical outcomes remains unknown. To overcome the limitations of individual trials in detecting differences in clinical outcomes, we performed a patient-level combined analysis of randomized trials in which radial-artery grafts were compared with saphenous-vein grafts for CABG.

Methods

RADIAL Project

The Radial Artery Database International Alliance (RADIAL) project was initiated in March 2015 by a group of clinical investigators conducting trials and research related to radial-artery grafting. One key aim of the project was to combine individual patient–level data from individual trials in which the use of the radial artery is compared with the use of other conduits for CABG to provide the basis for a combined analysis. The full list of the RADIAL investigators and the list of the detailed individual contributions to this study are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The authors vouch for the accuracy and completeness of the data presented.

Search Strategy and Trial Selection

The present analysis includes only randomized trials in which long-term (≥2 years) outcomes were assessed among patients who were randomly assigned to undergo either radial-artery grafting or saphenous-vein grafting to supplement left internal-thoracic-artery grafting during isolated CABG surgery. The full search strategy is described in the Supplementary Appendix.

After the identification of trials for inclusion, we compared trial protocols and publications from each trial and then provided a detailed specification of core minimum data requirements to each trial team to prepare the data for pooling. After receipt of the data, they were checked for missing values and for consistency. Data queries were resolved through direct consultation with each trial team before analysis. The most up-to-date follow-up information was also requested from the trial investigators. Renal insufficiency was defined as a preoperative serum creatinine level of more than 1.5 mg per deciliter (130 μmol per liter).[3]

The design of the analysis was published a priori on the International Prospective Register of Systematic Reviews (registration number, CRD42017077562). The present article was written in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

Outcomes

The primary outcome was a composite of major adverse cardiac events during follow-up and included death, myocardial infarction, and repeat revascularization. Each component of the composite outcome was also analyzed individually. Prespecified subgroup analyses of the primary outcome were performed according to age, sex, diabetes status, history of myocardial infarction, left ventricular ejection fraction (<35% or ≥35%), presence or absence of preoperative renal insufficiency, and radial-artery graft target vessel. The secondary outcome was graft patency at the protocol-defined follow-up angiographic examination. The patency rate was graded according to the FitzGibbon classification,[4] which grades graft patency as A (widely patent), B (flow limited), or O (occluded). For the purposes of our analysis, grades A and B were considered patent and grade O occluded.

Statistical Analysis

Baseline categorical variables were reported as counts and percentages and were compared with

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the use of a conditional regression analysis stratified according to trial. Baseline continuous variables were reported as means and standard deviations and were compared with a two-way analysis of variance stratified according to trial. Outcomes were reported as raw numbers and linearized event rates per 1000 patient-years to account for different follow-up durations among the trials. Cumulative incidences were determined and are presented graphically.

The primary analysis of clinical and angiographic end points was performed on the basis of the intention-to-treat principle with the use of a one-stage approach. Data were combined in a single data set and fitted in a Cox regression model stratified according to trial, with trial identifiers used as random effects. A competing-risk framework was used to compute pseudo–hazard ratios for myocardial infarction and repeat revascularization.[5] Treatment effects are presented as hazard ratios and 95% confidence intervals. The proportional-hazards assumptions were verified with the use of Schoenfeld residuals. Multivariable Cox models were implemented to investigate independent risk factors for graft occlusion, including baseline characteristics and the long-term use of agents for the prevention of arterial-graft spasm.

For the primary outcome, subgroup and interaction-term analyses were used to investigate the prespecified possible effect modifiers. A nonlinear relationship between age and treatment effect was 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 cutoff for the loss of benefit with the radial artery was evaluated with nonparametric computation of bootstrap pointwise confidence limits across a range of ages.

As a sensitivity analysis, the treatment effect on the primary outcome was reestimated in an as-treated analysis with a two-step approach. The as-treated analysis was implemented with the conduit received used as the treatment indicator, thus accounting for crossovers between treatment groups. For the two-stage approach, data on individual participants were first analyzed in each trial independently with Cox regression. This step produced aggregate data for each trial with a mean treatment effect estimate and its standard error. Aggregate data were then synthesized in the second step, in which the generic inverse variance method was used with a fixed effect when I^2 was less than 50% and a random effect when I^2 was greater than or equal to 50%. An influence analysis was used to assess the influence of individual trials on the final estimate. Publication bias was evaluated with the use of a funnel plot and linear regression test for asymmetry. In a sensitivity analysis of graft occlusion that included angiographic data from the Radial Artery Patency Study (RAPS), a mixed model based on graft type was used with individual trials as a random effect (see the Supplementary Appendix).

In a supplementary analysis, a generalized mixed-effects logistic regression with the original trials used as a random effect was performed to assess the effect of conduit selection on the risk of perioperative stroke. The saphenous-vein group was used as the reference in all analyses. All P values are two-sided. P values of less than 0.05 were considered to indicate statistical significance, without correction for multiple testing. Statistical analyses were performed with R software, version 3.2.3 (R Foundation).

RESULTS

TRIAL SELECTION

From 612 titles of articles, 38 pertinent trials were identified and included in a full-text review. After review, 32 trials were excluded because they did not meet the inclusion criteria. A total of 6 randomized trials were selected for the present analysis,[6-11] including a total of 1305 patients with 5266 patient-years of follow-up. Further details and the PRISMA flowchart and checklist are provided in Figure S1 and Table S1 in the Supplementary Appendix. An overview of the included trials is provided in Table 1. The principal investigators of the 6 individual trials were contacted, and all agreed to provide data on individual patients. The principal investigators of the Stand-in-Y trial also provided updated follow-up data.

Some of the individual trials had important design issues that were addressed before pooling of the data. In the Stand-in-Y trial, saphenous-vein grafts were compared with either radial-artery grafts or right internal-thoracic-artery

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Table 1. Trials Included in the Combined Analysis.*

Trial	Years of Enrollment	Country or Countries	No. of Patients	Radial-Artery Group	Saphenous-Vein Group	Radial-Artery Grafts to CCA	Mean Age	Male Sex	Clinical Follow-up Duration	Crossover	Follow-up Angiography	Median Time to Angiography
				no. of patients		%	*yr*	%	*yr*	%	*no. of patients*	*yr*
Petrovic et al.[10]†	2001–2003	Serbia	200	100	100	83	56.4±6.1	72.5	8	0	47	6
RAPCO[9]	1997–2004	Australia	225	113	112	100	72.8±4.7	80.9	5	3.6	84	5
RAPS[11]‡	1996–2001	Canada, New Zealand	269	269	269	49.8	60.4±8.0	84.8	8.4	2.6	269	7.7±1.5
RSVP[6]	1998–2000	United Kingdom	142	82	60	100	58.5±6.7	96.5	5.5	0	122	5.5
Stand-in-Y[7]	2003–2006	Italy	409	204	205	47	70.3±7.7	57.0	3.3	4.2	405	3.5
Yoo et al.[8]	2008–2009	Korea	60	35	25	98	75.7±5.4	50.0	5.8	0	41	0.7

* Plus–minus values are means ±SD. CCA denotes circumflex coronary artery, RAPCO Radial Artery Patency and Clinical Outcomes, and RSVP Radial Artery versus Saphenous Vein Patency.
† The trial by Petrovic et al. is not included in the analyses of graft occlusion.
‡ The Radial Artery Patency Study (RAPS) was not included in the analysis of clinical outcomes or in the main analysis of graft occlusion. Each patient in the trial received both a radial-artery graft and a saphenous-vein graft, and randomization was performed for the target coronary territory. The subset of 269 patients in this trial who underwent late angiography were included in the sensitivity analysis of graft occlusion.

grafts in different treatment groups.[7] The Radial Artery Patency and Clinical Outcomes (RAPCO) trial consisted of two separate trials, one of radial-artery grafts versus right internal-thoracic-artery grafts and one of radial-artery grafts versus saphenous-vein grafts.[9] For the present analysis, only patients who were included in the comparison between radial-artery grafts and saphenous-vein grafts were included from the Stand-in-Y and RAPCO trials. The trial by Petrovic et al. had no per-protocol angiographic examination, and patients underwent repeat angiographic examinations only for clinical indications.[10] The angiographic results of this trial were therefore not used for our analyses of graft occlusion. In RAPS, each patient received both a radial-artery graft and a saphenous-vein graft, and randomization was performed for the target coronary territory (i.e., "within-patient" randomization).[11] Because of the difficulty of attributing clinical events to the radial-artery graft or the saphenous-vein graft for any given patient, this trial was used only for the sensitivity analysis of graft occlusion (see the Supplementary Appendix).

COMBINED ANALYSIS

Overall, 534 patients who received radial-artery grafts and 502 patients who received saphenous-vein grafts were included in the comparison of clinical outcomes. The baseline characteristics of these patients are summarized in Table 2. Age, sex, diabetes prevalence, severe left ventricular dysfunction (left ventricular ejection fraction <35%), and the prevalence of renal insufficiency were similar in the two groups. Endoscopic harvesting of either the saphenous vein or the radial artery was not used in any trial. The total number of grafts performed was similar in the radial-artery group and the saphenous-vein group. The target vessel was the left circumflex coronary artery and the right coronary artery in approximately 75% and 25% of cases, respectively.

The main outcomes of the combined analysis are reported in Table 3. The mean (±SD) follow-up time was 60±30 months (median, 60; interquartile range, 39 to 83; range, 0 to 146). The incidence of the composite primary outcome of death, myocardial infarction, or repeat revascularization was significantly lower in the radial-artery group than in the saphenous-vein group (25 vs. 39 events per 1000 patient-years; hazard ratio, 0.67; 95% confidence interval [CI], 0.49 to

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Table 2. Characteristics of the Patients at Baseline.*

Characteristic	Radial-Artery Group (N=534)	Saphenous-Vein Group (N=502)	P Value
Age — yr	66.6±9.28	67.1±9.83	0.42
Female sex — no. (%)	158 (29.6)	151 (30.1)	0.92
Diabetes — no. (%)	181 (33.9)	177 (35.3)	0.69
Previous myocardial infarction — no. (%)	164 (30.7)	160 (31.9)	0.74
Elective admission — no. (%)	469 (87.8)	456 (90.8)	0.14
Renal insufficiency — no. (%)†	45 (8.4)	46 (9.2)	0.76
Left ventricular ejection fraction <35% — no. (%)	25 (4.7)	32 (6.4)	0.29
Target vessel — no. (%)			0.13
Left circumflex coronary artery	415 (77.7)	369 (73.5)	
Right coronary artery	119 (22.3)	133 (26.5)	
No. of grafts	3.1±0.65	3.1±0.55	0.53
Proximal anastomosis site — no. (%)			0.10
Ascending aorta	489 (91.6)	474 (94.4)	
Internal thoracic artery	45 (8.4)	28 (5.6)	

* Plus–minus values are means ±SD.
† Renal insufficiency was defined as a preoperative serum creatinine level of more than 1.5 mg per deciliter.[3]

Table 3. Main Outcomes.*

Outcome	Radial-Artery Group (N=534)		Saphenous-Vein Group (N=502)		Treatment Effect†	
	No. of Events (%)	Events per 1000 Patient-Yr‡	No. of Events (%)	Events per 1000 Patient-Yr‡	Hazard Ratio (95% CI)	P Value
Death, myocardial infarction, or repeat revascularization	67 (12.5)	25	94 (18.7)	39	0.67 (0.49–0.90)	0.01
Death	40 (7.5)	15	42 (8.4)	17	0.90 (0.59–1.41)	0.68
Myocardial infarction	16 (3.0)	6	21 (4.2)	9	0.72 (0.53–0.99)	0.04
Repeat revascularization	23 (4.3)	9	43 (8.6)	17	0.50 (0.40–0.63)	<0.001
Graft occlusion§	28/345 (8.1)	19	61/307 (19.9)	46	0.44 (0.28–0.70)	<0.001

* The analyses of clinical outcomes included all patients enrolled in the RAPCO, RSVP, Stand-in-Y, Yoo et al., and Petrovic et al. trials.
† Results are from a mixed-effect Cox regression model with individual trials included as a random effect (saphenous-vein group is the reference group).
‡ The total numbers of patient-years were 2675 in the radial-artery group and 2510 in the saphenous-vein group.
§ The main analysis of graft occlusion included all the patients with follow-up angiography with data available from the RAPCO, RSVP, Stand-in-Y, and Yoo et al. trials. Data were available for 345 of 434 radial-artery grafts (1454 patient-years) and 307 of 402 saphenous-vein grafts (1311 patient-years).

0.90; P=0.01) (Fig. 1A). Radial-artery grafts were associated with a nominally lower incidence of myocardial infarction (6 vs. 9 per 1000 patient-years; hazard ratio, 0.72; 95% CI, 0.53 to 0.99; P=0.04) and a lower incidence of repeat revascularization (9 vs. 17 per 1000 patient-years; hazard ratio, 0.50; 95% CI, 0.40 to 0.63; P<0.001) but not of death from any cause (15 and 17 per 1000 patient-years; hazard ratio, 0.90; 95% CI, 0.59 to 1.41; P=0.68) (Fig. S2 in the Supplementary Appendix).

A total of 345 of 434 patients (79%) in the radial-artery group and 307 of 402 patients (76%) in the saphenous-vein group underwent

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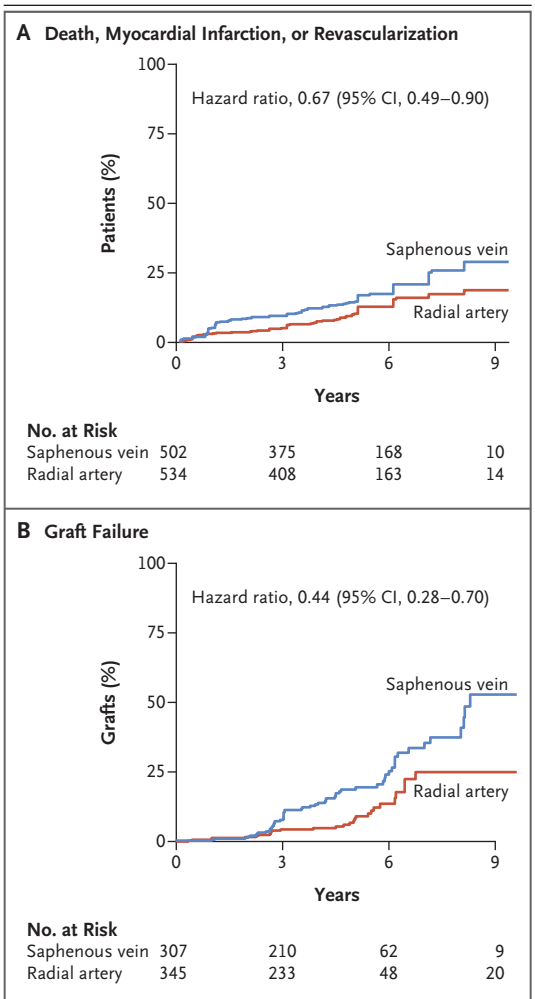

Figure 1. Cumulative Incidence of the Primary Composite Outcome of Death, Myocardial Infarction, or Repeat Revascularization and of Graft Failure in the Intention-to-Treat Analysis.

protocol-defined follow-up angiography. A comparison of the baseline characteristics between patients with follow-up angiographic data available and those without such data available is shown in Table S2 in the Supplementary Appendix. The mean follow-up time to protocol angiography was 50±30 months (median, 51; interquartile range, 29 to 68; range, 1 to 143). The incidence rates for graft occlusion were 19 events per 1000 patient-years in the radial-artery group versus 46 events per 1000 patient-years in the saphenous-vein group; radial-artery grafts were associated with a significantly lower risk of occlusion (hazard ratio, 0.44; 95% CI, 0.28 to 0.70; P<0.001) (Fig. 1B).

The results of the sensitivity analyses were consistent with the main analysis (Figs. S3, S4, and S5 and Table S3 in the Supplementary Appendix). A funnel plot of the included trials did not suggest evidence of publication bias (P=0.32) (Fig. S6 in the Supplementary Appendix). No significant difference in the rate of perioperative stroke was found between the two groups (0.7% in the radial-artery group and 1.4% in the saphenous-vein group; odds ratio, 0.71; 95% CI, 0.23 to 2.11; P=0.53).

SUBGROUP ANALYSES

A nominally significant interaction between age and the treatment effect on major adverse cardiac events was found (P=0.04), and an age of 75 years was identified as the cutoff for the loss of benefit from the radial artery. The interaction-term analysis (Fig. 2) showed a greater benefit with regard to major adverse cardiac events in association with radial-artery grafts than with saphenous-vein grafts in patients younger than 75 years of age (P=0.008), in women (P=0.01) and, nominally, in patients without renal insufficiency (P=0.02). Diabetes (P=0.35), a left ventricular ejection fraction of less than 35% (P=0.37), and previous myocardial infarction (P=0.45) did not modify the treatment effect. The radial-artery-graft target vessel did not significantly influence the treatment effect (P=0.42).

The risk factors for occlusion of radial-artery grafts and saphenous-vein grafts are shown in Table S4 in the Supplementary Appendix. Age was found to be an independent predictor of radial-artery-graft occlusion but not saphenous-vein-graft occlusion. Female sex was found to be associated with a lower risk of radial-artery-graft occlusion and higher risk of saphenous-vein-graft occlusion. Long-term use of calcium channel antagonist therapy was found to be associated with a nominally significantly lower risk of radial-artery-graft occlusion (details of the agents used to prevent arterial-graft spasm are provided in Table S5 in the Supplementary Appendix).

DISCUSSION

In this patient-level combined analysis of randomized, controlled trials comparing the radial artery and the saphenous vein as a second conduit for CABG, the use of radial-artery grafts was associated with a significantly lower risk of

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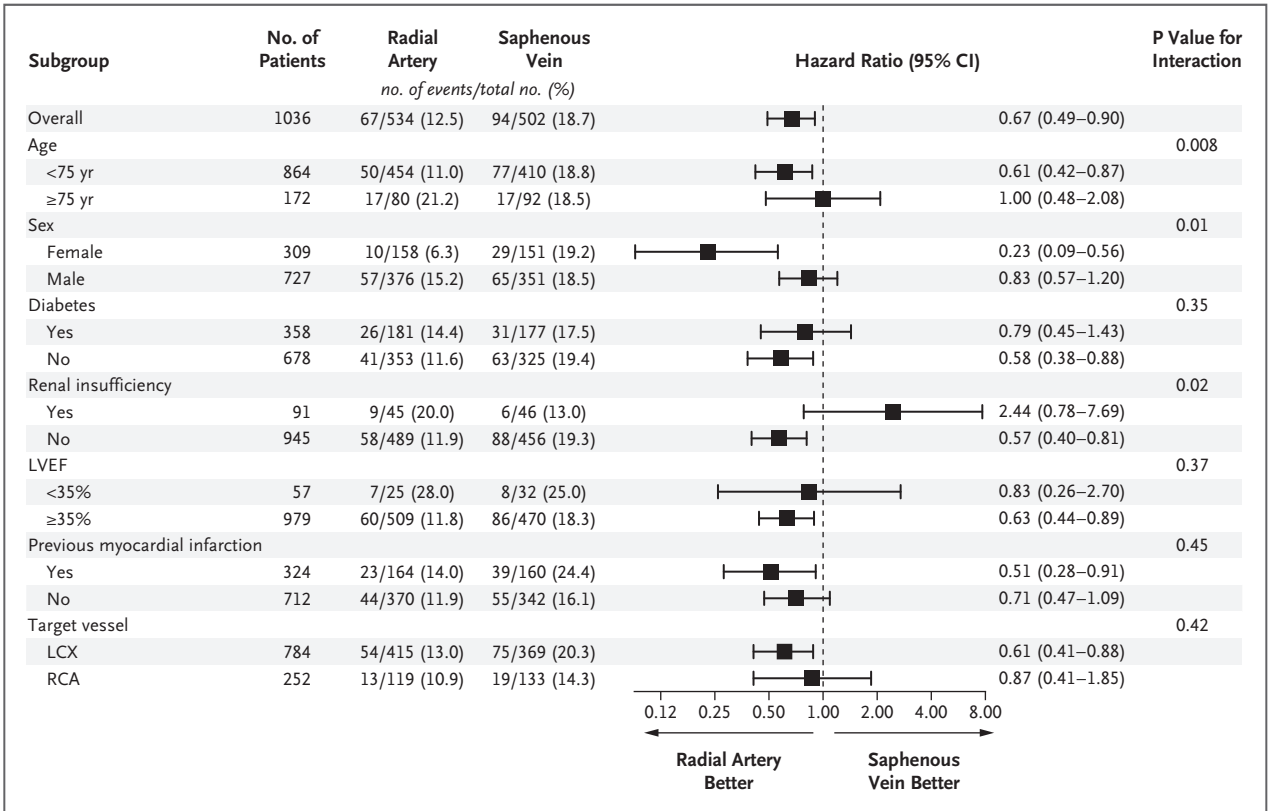

Figure 2. Subgroup Analyses and Interaction Terms for the Primary Composite Outcome of Death, Myocardial Infarction, or Repeat Revascularization.

The P values given are the P values for the interaction-term analyses. Renal insufficiency was defined as a preoperative serum creatinine level of more than 1.5 mg per deciliter.[3] LCX denotes left circumflex coronary artery, LVEF left ventricular ejection fraction, and RCA right coronary artery.

the composite outcome of death, myocardial infarction, or repeat revascularization and with a significantly lower risk of two individual components of the outcome — myocardial infarction and repeat revascularization — at a mean follow-up of 5 years. The use of radial-artery grafts was also associated with higher rates of angiographic patency at protocol-defined angiography, a finding that offers a biologic mechanism to explain the observed advantage in clinical outcomes.

The clinical benefit associated with the use of radial-artery grafts seemed more evident in patients younger than 75 years of age, in women, and in patients without renal insufficiency. The target vessel of the radial-artery graft was not found to be a significant effect modifier. Because the attrition rate of saphenous-vein grafts but not of radial-artery grafts increases almost exponentially with time,[12] it is as yet unknown whether the clinical difference in outcome that is apparent between the groups at 5 years could increase with a longer follow-up period.

The use of multiple arterial grafts is recommended by current guidelines and the position papers of professional societies, predominantly on the basis of large observational studies that have reported a benefit with regard to outcomes after CABG.[13-15] Despite these recommendations, arterial grafts have not been widely adopted; in the United States, less than 10% of patients who undergo elective CABG receive more than one arterial graft, and a radial-artery graft is used in less than 7%.[1] One of the reasons for their infrequent use is that the superior clinical outcomes associated with multiple arterial grafts that have been reported in registries have not been replicated in the randomized, controlled trials. There is concern that observational studies can be biased in favor of arterial conduits by unmatched confounders related to the unmeasurable (and un-

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matchable) judgment of the operating surgeons.[16] None of the randomized, controlled trials that compared radial-artery grafts with saphenous-vein grafts have individually shown a difference in clinical outcome.[6-11] The present patient-level combined analysis aimed to overcome the limitations of individual trials by pooling the data from those trials.

Our analysis also revealed that superior patency of radial-artery grafts did not translate into a significant difference in survival at 5 years. The traditional concept of a direct relationship between coronary graft patency and survival is both intuitive and biologically plausible and is indirectly supported by studies that show better survival among patients who receive a conduit with higher long-term patency when the graft is to the left anterior descending coronary artery.[17,18] However, although there is clear evidence that failure of grafts to the left anterior descending artery adversely affects survival, failure of grafts to other target vessels is more likely to result in nonfatal cardiac events.[19,20]

The present analysis has several limitations. Even when a combined-analysis approach is used, the overall number of patients is relatively small for a procedure as common as CABG. In addition, the patients who were enrolled in the six trials were highly selected. These aspects clearly limit the external validity of our work. The different trials used various surgical techniques, harvesting protocols, and postoperative secondary prevention regimens. Different trials also used various methods to evaluate the adverse events related to radial-artery harvesting, and a pooled analysis of data for this outcome was not possible. However, in all the individual trials, radial-artery harvesting was associated with only minor clinical symptoms and no overt hand-related complications.

There are also several limitations of the patency analysis in our study. In the main analysis, protocol-directed angiography was performed in only approximately three quarters of trial participants, and the patients for whom follow-up angiographic data were available differed in clinical characteristics and risk from patients for whom such data were not available. In addition, two trials accounted for more than two thirds of all the angiographic data. However, we found no heterogeneity across the included trials. The use of protocol-directed angiography renders the estimation of graft occlusion by means of clinically directed angiography difficult. Finally, the estimates of rates of repeat revascularization in angiographic trials may be inflated relative to those in clinical outcome studies, since repeat revascularization may be driven by angiographic findings rather than clinical findings.

In summary, in a pooled analysis of randomized, controlled trials comparing radial-artery grafts and saphenous-vein grafts as the second conduit for CABG, the use of radial-artery grafts resulted in a significantly lower rate of major adverse cardiac events and a better patency rate at a postoperative follow-up of 5 years.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. ElBardissi AW, Aranki SF, Sheng S, O'Brien SM, Greenberg CC, Gammie JS. Trends in isolated coronary artery bypass grafting: an analysis of the Society of Thoracic Surgeons adult cardiac surgery database. J Thorac Cardiovasc Surg 2012;143:273-81.
2. Gaudino M, Taggart D, Suma H, Puskas JD, Crea F, Massetti M. The choice of conduits in coronary artery bypass surgery. J Am Coll Cardiol 2015;66:1729-37.
3. Gowda S, Desai PB, Kulkarni SS, Hull VV, Math AAK, Vernekar SN. Markers of renal function tests. N Am J Med Sci 2010;2:170-3.
4. 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.
5. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
6. Collins P, Webb CM, Chong CF, Moat NE. Radial artery versus saphenous vein patency randomized trial: five-year angiographic follow-up. Circulation 2008;117:2859-64.
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. 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.
10. 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.

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11. Deb S, Cohen EA, Singh SK, Une D, Laupacis A, Fremes SE. 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.
12. 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.
13. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124(13):e652-e735.
14. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541-619.
15. Aldea GS, Bakaeen FG, Pal J, et al. The Society of Thoracic Surgeons clinical practice guidelines on arterial conduits for coronary artery bypass grafting. Ann Thorac Surg 2016;101:801-9.
16. Gaudino M, Di Franco A, Rahouma M, et al. Unmeasured confounders in observational studies comparing bilateral versus single internal thoracic artery for coronary artery bypass grafting: a meta-analysis. J Am Heart Assoc 2018;7(1):e008010.
17. Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. N Engl J Med 1986;314:1-6.
18. Garcia S, Sandoval Y, Roukoz H, et al. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. J Am Coll Cardiol 2013;62:1421-31.
19. Lopes RD, Mehta RH, Hafley GE, et al. Relationship between vein graft failure and subsequent clinical outcomes after coronary artery bypass surgery. Circulation 2012;125:749-56.
20. Shavadia J, Norris CM, Graham MM, Verma S, Ali I, Bainey KR. Symptomatic graft failure and impact on clinical outcome after coronary artery bypass grafting surgery: results from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry. Am Heart J 2015;169:833-40.
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