Associations Between Adding a Radial Artery Graft to Single and Bilateral Internal Thoracic Artery Grafts and Outcomes

Insights From the Arterial Revascularization Trial

BACKGROUND: Whether the use of the radial artery (RA) can improve clinical outcomes in coronary artery bypass graft surgery remains unclear. The ART (Arterial Revascularization Trial) was designed to compare survival after bilateral internal thoracic artery (BITA) over single left internal thoracic artery (SITA). In the ART, a large proportion of patients (≈20%) also received an RA graft instead of a saphenous vein graft (SVG). We aimed to investigate the associations between using the RA instead of an SVG to supplement SITA or BITA grafts and outcomes by performing a post hoc analysis of the ART.

METHODS: Patients enrolled in the ART (n=3102) were classified on the basis of conduits actually received (as treated). The analysis included 2737 patients who received an RA graft (RA group; n=632) or SVG only (SVG group; n=2105) in addition to SITA or BITA grafts. The primary end point was the composite of myocardial infarction, cardiovascular death, and repeat revascularization at 5 years. Propensity score matching and stratified Cox regression were used to compare the 2 strategies.

RESULTS: Myocardial infarction, cardiovascular death, and repeat revascularization cumulative incidence was 2.3% (95% confidence interval [CI], 1.1–3.4), 3.5% (95% CI, 2.1–5.0), and 4.4% (95% CI, 2.8–6.0) in the RA group and 3.4% (95% CI, 2.0–4.8), 4.0% (95% CI, 2.5–5.6), and 7.6% (95% CI, 5.5–9.7) in the SVG group, respectively. The composite end point was significantly lower in the RA group (8.8%; 95% CI, 6.5–11.0) compared with the SVG group (13.6%; 95% CI, 10.8–16.3; *P*=0.005). This association was present when an RA graft was used to supplement both SITA and BITA grafts (interaction *P*=0.62).

CONCLUSIONS: This post hoc ART analysis showed that an additional RA was associated with lower risk for midterm major adverse cardiac events when used to supplement SITA or BITA grafts.

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David P. Taggart, MD, PhD
Douglas G. Altman, DSc
Marcus Flather, MD
Stephen Gerry, MSc
Alastair Gray, PhD
Belinda Lees, BSc, PhD
Umberto Benedetto, MD, PhD
On Behalf of the ART (Arterial Revascularization Trial) Investigators

Correspondence to: Umberto Benedetto, MD, PhD, Bristol Heart Institute, University of Bristol, Senate House, Tyndall Avenue, Bristol, BS8 1TH, United Kingdom. E-mail umberto.benedetto@hotmail.com

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Clinical Perspective

What Is New?

- The use of a radial artery graft has been associated with superior angiographic patency rates compared with saphenous vein grafts, but the clinical impact of using the radial artery remains unclear.
- We found that the radial artery used to supplement either single or bilateral internal thoracic artery grafts instead of saphenous vein grafts only was associated with a significantly lower risk for major adverse cardiac events with a significantly lower rate of reintervention and marginally lower risk for cardiovascular death and subsequent myocardial infarction.

What Are the Clinical Implications?

- The radial artery graft is simple to perform because its caliber and handling properties are similar to those of vein grafts, and in view of its superior patency over saphenous vein grafts, it is an ideal conduit to achieve multiple arterial grafting and may improve patient outcomes.

Despite increasing interest in additional arterial conduits during coronary artery bypass graft (CABG) surgery,[1] the search for the optimum additional arterial conduit to supplement the left internal thoracic artery continues. The radial artery (RA) has been shown to provide better patency rates than saphenous vein grafts (SVGs),[2,3] but whether this translates into superior clinical outcomes remains unclear. A few randomized controlled trials investigating the effect of RA grafts on clinical outcomes were underpowered to detect differences in clinical outcomes.[4–6] On the other hand, observational studies that have focused only on survival have reported discordant results.[7–16]

The ART (Arterial Revascularization Trial) was designed to compare survival after bilateral internal thoracic artery (BITA) versus single left internal thoracic artery (SITA). The interim midterm results (5 years) demonstrated no difference between the groups.[1] A large proportion of the ART patients (≈20%) received the RA as a second conduit to supplement an SITA graft or as a third conduit to supplement BITA grafts, making the ART the largest series of RA grafting in the context of a randomized trial involving SITA or BITA.

We aimed to investigate the associations between the use of an RA graft to supplement either SITA or BITA grafts and clinical outcomes by performing a post hoc analysis of the ART.

METHODS

The present study is a post hoc analysis of 5-year outcomes of the ART. This research adheres to the principles set forth in the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html). In the ART, the use of the RA was based on surgeon's discretion. For the purpose of the present analysis, patients enrolled in the ART (n=3102) were classified on the basis of conduits actually received (as-treated principle). The present analyses compared the strategy using the RA with or without additional SVG (RA group) versus SVG only (SVG group) to supplement SITA or BITA grafts.

The following patients were excluded from the present analyses: those in whom neither SVG nor RA was used (n=328), patients receiving SVG but neither SITA nor BITA graft (n=30), and patients receiving an RA graft but neither SITA nor BITA used (n=7).

Trial Design

The ART was approved by the institutional review board of all participating centers, and informed consent was obtained from each participant. The protocol for the ART has been published.[17] Briefly, the ART is a 2-arm, randomized multicenter trial conducted in 28 hospitals in 7 countries, with patients being randomized equally to SITA or BITA grafts. Eligible patients were those with multivessel coronary artery disease undergoing CABG, including urgent patients, with grafting recommended in case of target stenosis ≥75%. Only emergency patients (refractory myocardial ischemia/cardiogenic shock) and those requiring single grafts or redo CABG were excluded.

Follow-Up

Questionnaires were sent to study participants by post at 6 months and every year after surgery. No clinic visits were planned apart from the routine clinical 6-week postoperative visit. Participants were sent stamped, addressed envelopes to improve the return rates of postal questionnaires. Study coordinators contacted participants by telephone to alert them of the arrival of the questionnaire and to ask them about medications, adverse events, and health services resource use.

Study Outcomes

The primary outcome for this analysis was the composite of major adverse cardiac events (MACEs) at 5 years, including cardiovascular death, myocardial infarction (MI), and repeat revascularization. The associations between the use of an RA graft and MACE individual components and overall mortality were also investigated.

Hospital outcomes analyzed were hospital mortality, return to the operating room, postoperative intra-aortic balloon pump, renal replacement therapy, sternal wound infection, MI, cerebrovascular accident, repeat revascularization, and postoperative atrial fibrillation. Adverse events were adjudicated by members of the Clinical Event Review Committee who were blinded to the surgical procedure.

Statistical Analysis

For baseline characteristics, variables are summarized as mean and SD for continuous variables and as percentage for categorical variables. Multiple imputation (m=3) was used to address missing data. The Rubin[18] method was used to combine

results from each of m imputed data sets (Amelia R package). Because of a lack of randomization with regard to receiving RA, a propensity score was generated for each patient from a multivariable logistic regression model based on pretreatment covariables as independent variables with RA versus SVG as a binary dependent variable.[19] Covariables included in the propensity score model were age, female sex, body mass index, systolic and diastolic blood pressures at admission, creatinine, New York Heart Association functional class, unstable angina, treated hypertension, treated hyperlipidemia, diabetes mellitus, smoking, chronic obstructive pulmonary disease, peripheral vascular disease, transient ischemic attack, cerebrovascular accident, MI, percutaneous coronary intervention, atrial fibrillation, left ventricular ejection fraction, dual antiplatelet therapy, off-pump surgery, BITA, left main stem disease, left anterior descending artery disease, circumflex artery disease, diagonal branch disease, and right coronary artery disease. Pairs of patients were derived with greedy 1:1 matching with a caliper of width of 0.2 SD of the logit of the propensity score (nonrandom R package). The quality of the match was assessed by comparing selected pretreatment variables in propensity score–matched patients using the standardized mean difference, for which an absolute standardized difference of >10% is suggested to represent meaningful covariable imbalance. The McNemar test and paired *t* test were used to assess the statistical significance of the risk difference in short-term outcomes in the matched sample.[19] A Cox regression model, stratified on the matched pairs,[19] was used to estimate the associations between treatment and the primary outcome and overall mortality. This approach accounts for the within-pair homogeneity by allowing the baseline hazard function to vary across matched sets (survival R package). Competing-risk analysis (prodlim and riskRegression R packages) was used to estimate the associations between treatment and the primary end point individual components. As sensitivity analysis, the associations between the use of an RA graft and outcomes were tested in a mixed-effect Cox model to account for clustering effect resulting from individual surgeons and centers[20] (http://CRAN.R-project.org/package=coxme). The association between use of an RA graft and outcomes was also adjusted for medication at discharge, including aspirin, clopidogrel, β-blockers, calcium channel antagonists (CCAs), statins, and angiotensin-converting enzyme inhibitors and angiotensin receptors blockers. Finally, possible modifiers of associations tested with interaction analyses were age <70 and ≥70 years, female versus male sex, diabetes mellitus versus no diabetes mellitus, reduced versus preserved left ventricular ejection fraction, SITA versus BITA graft, and off- versus on-pump surgery.

All *P* values were 2 sided, with $P<0.05$ considered to indicate statistical significance. All statistical analyses were performed with R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Sample

The final population included 2737 patients who received an RA graft (RA group; n=632) or SVG only (SVG group; n=2105). Among those who received an RA graft, SITA graft was used in 359 patients (57%) and BITA graft was used in 273 patients (43%). In the RA group, 397 patients (63%) underwent total arterial revascularization, whereas the remaining 235 (37%) received at least 1 additional SVG. In the SVG group, 1330 patients (63%) had SITA graft and the remaining 775 (37%) had BITA graft.

Graft Configuration and Target Details

Graft configurations and target characteristics in the RA and SVG groups are summarized in Table 1. Overall, the quality (including size and need for endarterectomy) of targets grafted with the RA was not superior to that of targets grafted with SVG in the SVG group. Table I in the online-only Data Supplement summarizes graft configuration and target details in subjects receiving an RA graft to supplement SITA and BITA grafts. When the RA was used to supplement an SITA graft, it was preferentially used to graft the circumflex artery (65%), followed by the right coronary artery (22%). When the RA was used to supplement BITA grafts, it was preferentially used to graft the right coronary artery (64%), followed by the circumflex artery (25%).

RA Use Variation Across Surgeons and Centers

The present post hoc analysis included a total of 157 participating surgeons and 28 cardiac centers. The use of the RA over SVG significantly varied only across surgeons (Figure I in the online-only Data Supplement; information not available in 120 cases marked as 1) and across different centers (Figure II in the online-only Data Supplement).

Propensity Score Matching

Before matching, the RA and SVG groups showed significant differences in terms of preoperative nitrate administration, age, functional New York Heart Association class, rate of BITA graft use, body mass index, diabetes mellitus, and preoperative left ventricular ejection fraction. Patients receiving the RA were 2 years younger and more likely to have insulin-treated diabetes mellitus and decreased left ventricular ejection fraction. After propensity score matching, the 2 groups were comparable for all pretreatment characteristics (Table 2 and Figure 1).

Hospital Outcomes

Hospital outcomes are reported in Table 3. Mortality rates and postoperative complications were comparable between the 2 groups.

Table 1. Conduits and Relative Targets Details in the Radial Artery and Saphenous Vein Graft Groups

	Left Internal Thoracic Artery	Other	Radial Artery	Right Internal Thoracic Artery	Saphenous Vein Graft
Radial artery group (n=632)					
Conduits used, n	627	4	362	278	235
Distal anastomosis, n	700	4	789	291	316
Sequential anastomosis, n (%)	131 (18.7)	2 (50.0)	163 (20.7)	27 (9.3)	21 (6.6)
Proximal anastomosis,* n (%)					
Aorta	34 (16.3)	1 (25.0)	574 (73.4)	20 (16.8)	304 (97.1)
Other conduit	175 (83.7)	3 (75.0)	208 (26.6)	99 (83.2)	9 (2.9)
Target, n (%)					
Circumflex	130 (18.6)	2 (50.0)	394 (49.9)	123 (42.3)	75 (23.7)
Diagonal branch	75 (10.7)	0 (0.0)	75 (9.5)	21 (7.2)	57 (18.0)
Left anterior descending artery	493 (70.4)	0 (0.0)	24 (3.0)	133 (45.7)	2 (0.6)
Right coronary artery	2 (0.3)	2 (50.0)	296 (37.5)	14 (4.8)	182 (57.6)
Vessel diameter, mean (SD), mm	1.79 (0.35)	1.75 (0.20)	1.73 (0.38)	1.79 (0.37)	1.70 (0.33)
Vessel quality, n (%)					
Good	287 (41.5)	2 (50.0)	296 (37.9)	102 (35.5)	141 (45.8)
Satisfactory	327 (47.3)	1 (25.0)	419 (53.6)	144 (50.2)	135 (43.8)
Poor	78 (11.3)	1 (25.0)	66 (8.5)	41 (14.3)	32 (10.4)
Endarterectomy n (%)	1 (0.1)	0 (0.0)	10 (1.3)	4 (1.4)	2 (0.6)
Saphenous vein graft group (n=2105)					
Conduits used, n	2079	0	0	801	2015
Distal anastomosis, n	2221	0	0	825	3877
Sequential anastomosis, n (%)	182 (8.2)	…	…	43 (5.2)	271 (7.0)
Proximal anastomosis,* n (%)					
Aorta	48 (16.7)	…	…	66 (22.2)	3713 (96.2)
Other conduit	237 (82.3)	…	…	229 (77.1)	145 (3.8)
Target, n (%)					
Circumflex	356 (16.0)			377 (45.7)	1673 (43.2)
Diagonal branch	176 (7.9)	…	…	53 (6.4)	480 (12.4)
Left anterior descending artery	1687 (76.0)	…	…	378 (45.8)	71 (1.8)
Right coronary artery	2 (0.1)	…	…	17 (2.1)	1653 (42.6)
Vessel diameter, mean (SD), mm	1.86 (0.46)	…	…	1.87 (0.44)	1.83 (0.51)
Vessel quality, n (%)					
Good	1048 (48.1)	…	…	397 (49.2)	1816 (47.7)
Satisfactory	813 (37.3)	…	…	295 (36.6)	1555 (40.9)
Poor	317 (14.6)	…	…	115 (14.3)	433 (11.4)
Endarterectomy, n (%)	10 (0.5)	…	…	3 (0.4)	32 (0.8)

*For left and right internal thoracic arteries, numbers refer to non–in situ configuration.

Outcomes at 5 Years

The 5-year outcomes are reported in Table 4. The rate of MACEs was 8.8% (95% confidence interval [CI], 6.5–11.0) versus 13.6% (95% CI, 10.8–16.3) in the RA and SVG groups, respectively. The use of an RA graft was associated with significantly lower risk for MACEs (hazard ratio [HR], 0.60; 95% CI, 0.41–0.85; *P*=0.005). This result was mainly determined by a significantly lower risk for repeat revascularization in the RA group (4.4%; 95% CI, 2.8–6.0) compared with the SVG group (7.6%; 95% CI, 5.5–9.7) (HR, 0.59; 95% CI, 0.36–0.95; *P*=0.03; Figure 2). Compared with the SVG group, the RA group had a nonsignificantly lower risk of MI (HR, 0.68; 95% CI, 0.34–1.38; *P*=0.30), cardiovascular death (HR, 0.83;

Table 2. Baseline Characteristics in the Radial Artery and Unmatched and Matched Saphenous Vein Graft Group With Relative *P* Values and Standardized Mean Difference

	Radial Artery Group	Saphenous Vein Graft Group (Unmatched)	*P*	Standardized Mean Difference, %	Saphenous Vein Graft Group (Matched)	*P*	Standardized Mean Difference, %
n	632	2105			632		
Age, mean (SD)	62 (9)	64 (9)	<0.001	19	63 (9)	0.5	4
Female, n (%)	80 (12.7)	288 (13.7)	0.5	3	80 (12.7)	1.0	0
Body mass index, mean (SD), kg/m^2	29 (4)	28 (4)	0.006	12	29 (4)	0.3	6
Systolic blood pressure, mean (SD), mm Hg	133 (19)	132 (18)	0.3	5	132 (18)	0.7	2
Diastolic blood pressure, mean (SD), mm Hg	75 (11)	75 (11)	1	0	74 (11)	0.3	6
Creatinine, mean (SD), mg/dL	1.1 (0.2)	1.1 (0.3)	0.2	6	1.1 (0.2)	0.7	2
New York Heart Association class III/IV, n (%)	106 (16.8)	478 (22.7)	0.002	15	102 (16.1)	0.8	2
Unstable angina, n (%)	41 (6.5)	166 (7.9)	0.3	6	48 (7.6)	0.5	4
Treated hypertension, n (%)	471 (74.5)	1653 (78.5)	0.04	10	471 (74.5)	1.0	0
Treated hyperlipidemia, n (%)	588 (93.0)	1981 (94.1)	0.4	4	590 (93.4)	0.9	2
Diabetes mellitus, n (%)			0.1	1		1.0	1
No history of diabetes mellitus	465 (73.6)	1614 (76.7)			461 (72.9)		
Insulin-treated diabetes mellitus	46 (7.3)	106 (5.0)			47 (7.4)		
Non–insulin-treated diabetes mellitus	121 (19.1)	385 (18.3)			124 (19.6)		
Smoking, n (%)			0.5	6		0.9	3
Current smoking	94 (14.9)	290 (13.8)			89 (14.1)		
Ex-smoker	345 (54.6)	1207 (57.3)			351 (55.5)		
Never smoked	193 (30.5)	608 (28.9)			192 (30.4)		
Chronic obstructive pulmonary disease, n (%)	11 (1.7)	60 (2.9)	0.2	7	12 (1.9)	1.0	1
Asthma, n (%)	30 (4.7)	88 (4.2)	0.6	3	28 (4.4)	0.9	2
Peripheral vascular disease, n (%)	45 (7.1)	148 (7.0)	1.0	0	51 (8.1)	0.6	4
Transient ischemic attack, n (%)	19 (3.0)	85 (4.0)	0.3	6	13 (2.1)	0.4	6
Cerebrovascular accident, n (%)	15 (2.4)	67 (3.2)	0.4	5	12 (1.9)	0.7	3
Myocardial infarction, n (%)	260 (41.1)	891 (42.3)	0.6	2	269 (42.6)	0.7	3
Percutaneous coronary intervention, n (%)	86 (13.6)	332 (15.8)	0.2	6	91 (14.4)	0.8	2
Preoperative atrial fibrillation, n (%)	8 (1.3)	32 (1.5)	0.8	2	11 (1.7)	0.64	0.039
Left ventricular ejection fraction preoperative, n (%)			0.1	10		0.9	3
≥50%	454 (71.8)	1602 (76.1)			446 (70.6)		
31%–49%	163 (25.8)	456 (21.7)			170 (26.9)		
≤30%	15 (2.4)	47 (2.2)			16 (2.5)		
Before dual antiplatelet therapy , n (%)	135 (21.4)	484 (23.0)	0.4	4	152 (24.1)	0.3	6
Antiplatelet within 3 d, n (%)	96 (15.2)	350 (16.6)	0.4	4	91 (14.4)	0.8	2
Nitrates preoperative, n (%)	249 (39.4)	1079 (51.3)	<0.001	24	255 (40.3)	0.8	2
Off-pump coronary artery bypass, n (%)	239 (37.8)	842 (40.0)	0.4	5	247 (39.1)	0.7	3
Bilateral internal thoracic artery, n (%)	273 (43.2)	775 (36.8)	0.004	13	272 (43.0)	1.0	0
Left main stem disease, n (%)	142 (22.5)	410 (19.5)	0.1	7	134 (21.2)	0.6	3
Left anterior descending artery, n (%)	625 (98.9)	2073 (98.5)	0.6	4	625 (98.9)	1.0	0
Circumflex, n (%)	581 (91.9)	1952 (92.7)	0.6	3	576 (91.1)	0.7	3
Diagonal, n (%)	221 (35.0)	691 (32.8)	0.3	5	228 (36.1)	0.7	2
Right coronary artery, n (%)	469 (74.2)	1598 (75.9)	0.4	4	473 (74.8)	0.9	2

(*Continued*)

Table 2. Continued

	Radial Artery Group	Saphenous Vein Graft Group (Unmatched)	*P*	Standardized Mean Difference, %	Saphenous Vein Graft Group (Matched)	*P*	Standardized Mean Difference, %
Grafts, n (%)			0.8	5		0.8	7
2	69 (10.9)	246 (11.7)			78 (12.3)		
3	332 (52.5)	1119 (53.2)			314 (49.7)		
4	191 (30.2)	630 (29.9)			201 (31.8)		
5	38 (6.0)	104 (4.9)			36 (5.7)		
6	2 (0.3)	6 (0.3)			3 (0.5)		

95% CI, 0.46–1.51; *P*=0.55), and overall death (HR, 0.83; 95% CI, 0.54–1.27; *P*=0.39). The use of an RA graft remained associated with a lower incidence of MACEs when the analysis also accounted for the clustering by individual surgeons (mixed-effect HR, 0.55; 95% CI, 0.35–0.87; *P*=0.01) and hospital (mixed-effect HR, 0.59; 95% CI, 0.41–0.86; *P*=0.005). When the analysis was restricted to patients requiring grafts only to the left coronary system, there was a larger but not significantly lower risk for the RA group (HR, 0.25; 95% CI, 0.05–1.17). We saw no associations with better outcomes using an RA graft without additional SVG (HR, 0.71; 95% CI, 0.46–1.10) compared with an RA with additional SVG (HR, 0.40; 95% CI, 0.20–0.78).

Postoperative Medications

Medications prescribed at discharge are reported in Table II in the online-only Data Supplement. Patients receiving an RA graft were more likely to be discharged on CCAs, although only 29% of them received CCAs. At 5-year follow-up, only 112 patients in the RA group were on CCAs, of whom 44 patients were initially discharged on CCAs. Patients in the SVG group were more likely to be discharged on dual antiplatelet therapy with clopidogrel. After adjustment for medications prescribed at discharge, the use of the RA remained associated with lower 5-year MACE rates (adjusted HR, 0.59; 95% CI, 0.39–0.91; *P*=0.01). Among patients receiving an RA graft, CCA prescribed at discharge was associat-

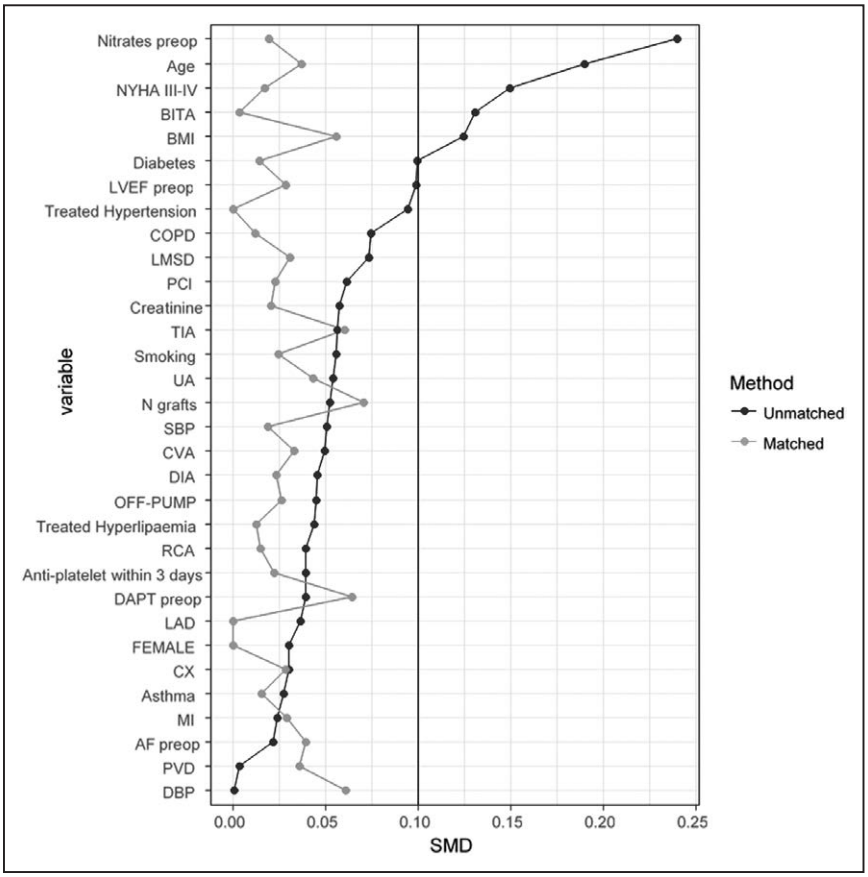

Figure 1. Changes in standardized mean difference (SMD) between the radial artery and saphenous vein graft groups before and after propensity score matching. AF indicates atrial fibrillation; BITA, bilateral internal thoracic artery; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; CX, circumflex disease; DAPT, dual antiplatelet therapy; DBP, diastolic blood pressure; DIA, diagonal branch disease; LAD, left anterior descending artery disease; LMSD, left main stem disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery disease; SBP, systolic blood pressure; TIA, transient ischemic attack; and UA, unstable angina.

Table 3. Hospital Outcomes

	Radial Artery Group	Saphenous Vein Graft Group (Unmatched)	P*	Saphenous Vein Graft Group (Matched)	P†
n	632	2105		632	
Death, n (%)	9 (1.4)	20 (1.0)	0.42	5 (0.8)	0.42
Return to operating room, n (%)	27 (4.3)	72 (3.4)	0.38	19 (3.0)	0.29
Intra-aortic balloon post, n (%)	21 (3.3)	91 (4.3)	0.32	29 (4.6)	0.31
Renal replacement therapy, n (%)	45 (7.1)	100 (4.8)	0.03	36 (5.7)	0.36
Sternal wound infection, n (%)	25 (4.0)	67 (3.2)	0.41	19 (3.0)	0.44
Myocardial infarction, n (%)	6 (0.9)	40 (1.9)	0.15	15 (2.4)	0.08
Cerebral vascular accident, n (%)	5 (0.8)	31 (1.5)	0.26	5 (0.8)	1.00
Repeat revascularization, n (%)	2 (0.3)	13 (0.6)	0.55	5 (0.8)	0.45
Postoperative atrial fibrillation, n (%)	152 (24.1)	524 (24.9)	0.71	165 (26.1)	0.44

*The χ^2 test (binary outcomes) and paired *t* test (continuous outcomes).
†The McNemar test (binary outcomes) and paired *t* test (continuous outcomes).

ed with a numerically lower incidence of MACEs (5.2% versus 10.2%; *P*=0.2; Figure 3).

Modifiers of the Associations Between RA Graft Use and Outcomes

None of possible modifiers of association investigated was found to influence the associations between RA graft use and MACEs compared with SVG only (Figure 4). Subgroup analysis showed that the association between the RA and lower risk of MACEs was present for both SITA and BITA grafts (interaction *P*=0.62; Table III and Figures III and IV in the online-only Data Supplement).

Angiographic Follow-Up

Angiographic follow-up was performed only in symptomatic patients; therefore, patency rates of different conduits could not be analyzed. For those who underwent repeat revascularization, clinical presentation and revascularization strategy adopted were not available in all cases. In the RA group, graft failure and native coronary disease progression were documented in 4 and 21 cases, respectively, among 27 cases of repeat revascularization. In the SVG group, graft failure and native coronary disease progression were documented in 54 and 90 cases, respectively, among 152 cases of repeat revascularization. All failed grafts were reported to be SVG. In the RA group, need for repeat CABG and repeat percutaneous coronary intervention was documented in 2 and 23 cases, respectively. In the SVG group, need for repeat CABG and repeat percutaneous coronary intervention was documented in 6 and 113 cases, respectively.

DISCUSSION

The main finding of the present analysis is that an RA graft (with or without additional vein graft) used to supplement either SITA and BITA grafts, instead of SVG only, was associated with significantly lower risk for major adverse cardiac events with a significantly lower rate of reintervention and marginally lower risk for cardiovascular death and subsequent MI, despite the fact that the quality of RA targets was not superior to that of SVG targets. On the other hand, use of an RA graft did not increase operative mortality or complications.

Although several randomized trials have shown that use of an RA graft is associated with superior 5-year patency rates compared with SVGs,[3,4] whether this translates into better clinical outcomes remains uncertain. In fact, randomized controlled trials conducted to date are limited by small sample sizes, and the results are incon-

Table 4. The 5-Year Outcomes Rates With 95% Confidence Intervals

	Radial Artery Group, n (%) [95% CI]	Saphenous Vein Graft Group (Unmatched), n (%) [95% CI]	P*	Saphenous Vein Graft Group (Matched), n (%) [95% CI]	P†
n	632	2105		632	
Myocardial infarction	14 (2.3) [1.1–3.4]	78 (3.7) [2.9–4.6]	0.07	21 (3.4) [2.0–4.8]	0.30
Repeat revascularization	27 (4.4) [2.8–6.0]	152 (7.3) [6.2–8.5]	0.008	47 (7.6) [5.5–9.7]	0.033
Cardiovascular death	22 (3.5) [2.1–5.0]	73 (3.5) [2.7–4.3]	0.99	25 (4.0) [2.5–5.6]	0.55
Overall death	45 (7.3) [5.2–9.3]	189 (9.2) [7.9–10.4]	0.15	51 (8.3) [6.1–10.5]	0.39
Cardiovascular death/myocardial infarction/repeat revascularization	53 (8.8) [6.5–11.0]	261 (12.9) [11.4–14.3]	0.005	82 (13.6) [10.8–16.3]	0.005

CI indicates confidence interval.
*Unadjusted Cox model.
†Cox model stratified for matched pairs.

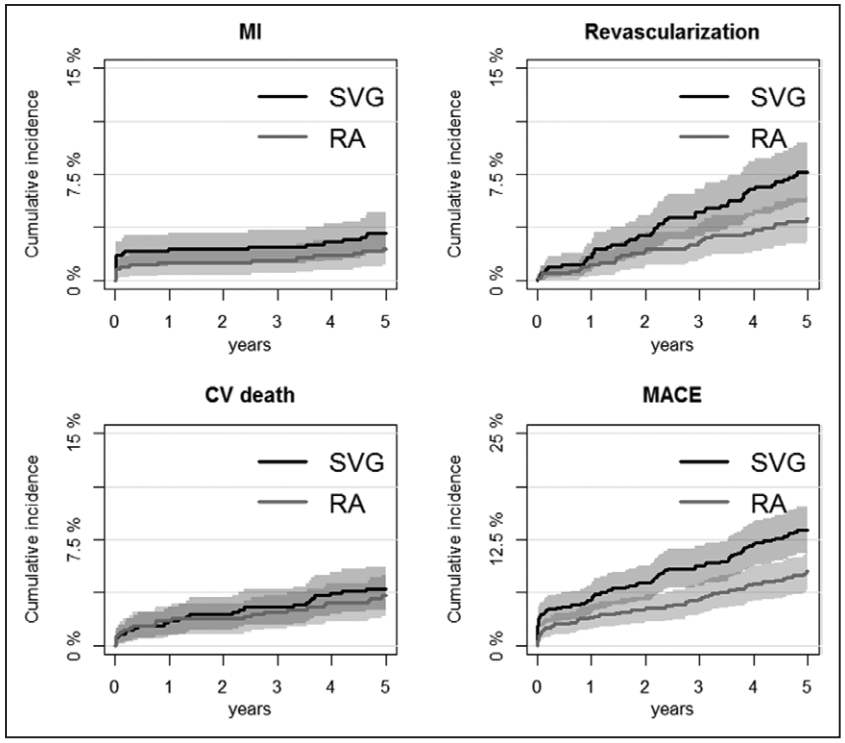

Figure 2. Cumulative incidence of myocardial infarction (MI), revascularization, cardiovascular (CV) death, and the composite of major adverse cardiac events (MACE) in the radial artery (RA) and saphenous vein graft (SVG) group after matching.

clusive. The RSVP randomized trial (Radial Artery Versus Saphenous Vein Patency)[4] compared 82 and 60 patients randomized to receive the SITA and RA grafts or SITA and SVGs. The only robust clinical outcome assessed was mortality. The 5-year survival rate was 94.4%, with no significant difference in survival between the 2 groups. In the RAPCO Study (Radial Artery Patency and Clinical Outcome),[5] patients ≥70 years of age were randomly assigned to receive either SITA and RA grafts (n=73) or SITA and SVGs grafts (n=80). At the 5-year follow-up, cardiac event–free survival rates were 84% for the RA subgroup and 89% for the SVG subgroup (*P*=0.9). Petrovic et al[6] randomized 200 patients to receive either SITA and RA grafts or SITA and SVGs. They found no difference in 8 year clinical outcomes. In a larger trial by Goldman et al,[21] 757 patients were randomly assigned to receive either SITA and RA grafts (n=366) or SITA and SVGs grafts (n=367). There was no significant difference between the 2 groups at 1 year in terms of death, MI, stroke, and repeat coronary revascularization. However, outcomes beyond 1 year are not available.

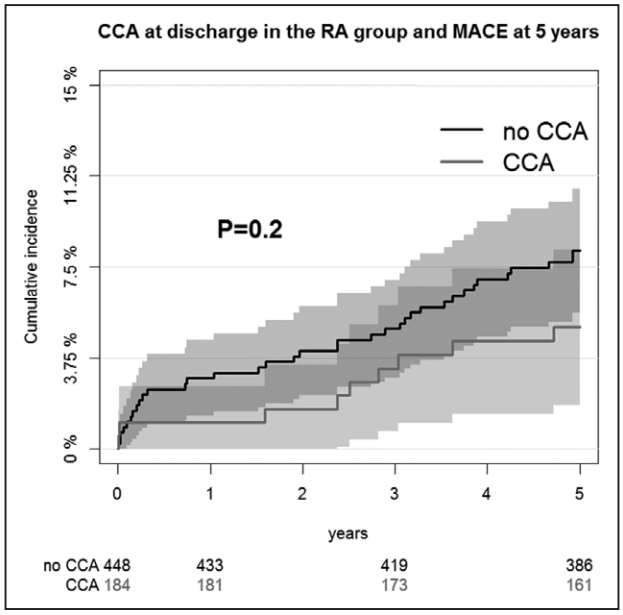

Figure 3. Cumulative incidence of the composite of major adverse cardiac events (MACE) in the radial artery (RA) according to calcium channel antagonists (CCA) prescribed at discharge.

On the other hand, several retrospective studies that investigated the associations between the use of RA as an additional arterial conduit instead of SVG and outcomes reported discordant results for survival. Schwann et al[7] compared SITA+RA and SITA+SVG in 2 institutional US cohorts. Kaplan-Meier survival was significantly better for RA grafting (*P*<0.001). Hayward et al[8] compared 1832 patients who received at least 1 RA graft in addition to SITA with 749 (29%) who received SITA and veins only from a multicenter database. At 7 years, survival rates between the RA and SVG groups were similar (75% for RA versus 74% for SVG; *P*=0.65). A few studies have investigated the associations between the use of RA grafts and survival in the context of BITA grafting with conflicting results. Di Mauro and colleagues[12] reported survival at 8 years of 92% among 87 patients undergoing BITA+RA grafting and 96% among patients undergoing BITA+SVG (*P*=0.12). More recently, Grau and coworkers[13] published a series of 183 patients undergoing BITA+RA grafting.

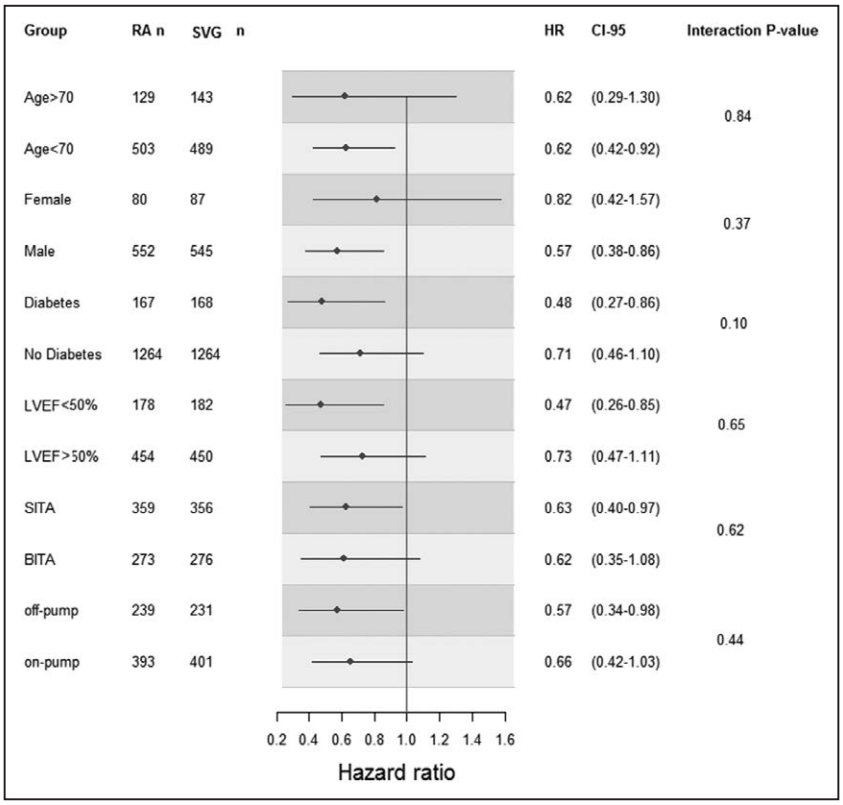

Figure 4. Subgroup analysis and interaction analysis on the effect of the radial artery (RA) over saphenous vein graft (SVG) on the composite of major adverse cardiac events (MACE).
BITA indicates bilateral internal thoracic artery; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; and SITA, single left internal thoracic artery.

Long-term survival in the BITA+RA groups was comparable to that in the BITA+SVG groups (*P*=0.25). Mohammadi and associates[14] have reported comparable long-term survival in 249 matched pairs of patients undergoing BITA+RA versus BITA+SVG (*P*=0.44). Shi et al[15] compared 262 matched patient pairs of BITA+RA and BITA+SVG. At 15 years, BITA + RA patients experienced better risk-adjusted survival (82% versus 72%; *P*=0.02). Finally, we have reported a longer-term survival comparison in 275 matched patient pairs of BITA+RA and BITA+SVG from a single institution,[16] and the 2 groups showed comparable 15-year survival rates (log-rank *P*=0.54).

The present post hoc ART analyses support the hypothesis that an additional RA may reduce midterm major adverse cardiac events when used to supplement either SITA or BITA grafts compared with SVG only. The better clinical outcomes observed in patients receiving an RA graft can be attributed to its superior patency rate compared with SVG.[2,3,22]

An interim analysis of the ART[1] has shown that BITA grafts did not improve 5-year outcomes compared with an SITA strategy. However, the primary end point of the ART is 10-year survival, and those data will be needed to draw any conclusions on whether there is any potential benefit of BITA grafts over the longer term. Previous studies have supported the hypothesis that the beneficial effect from BITA on clinical outcomes may be delayed by as much as 7 to 10 years.[23] On the other hand, the RA graft is simple to perform because its caliber and handling properties are similar to those of vein grafts. The superior patency rate of the RA over SVG at 5 years has been demonstrated by several randomized controlled trials,[2] and the use of an RA graft has been reported to exhibit maximal benefit between 0.5 and 5 years.[7]

The main limitations of the present analyses are the nonrandomized comparison and the low number of outcome events. Propensity score modeling included several variables, but we cannot exclude a residual selection bias based on a unmeasured or unmeasurable characteristics.

CONCLUSIONS

The present post hoc analysis of the ART showed that the use of an additional RA graft to supplement both SITA and BITA grafts was associated with a lower risk for MACEs at 5 years. From these results, it seems reasonable to consider the use of an RA graft a valid option for multiple arterial grafting.

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From Nuffield Department of Surgery, University of Oxford, John Radcliffe Hospital, United Kingdom (D.P.T., B.L.); Centre

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FOOTNOTES

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REFERENCES

1. Taggart DP, Altman DG, Gray AM, Lees B, Gerry S, Benedetto U, Flather M; ART Investigators. Randomized trial of bilateral versus single internal-thoracic-artery grafts. *N Engl J Med*. 2016;375:2540–2549. doi: 10.1056/NEJMoa1610021.
2. Cao C, Manganas C, Horton M, Bannon P, Munkholm-Larsen S, Ang SC, Yan TD. Angiographic outcomes of radial artery versus saphenous vein in coronary artery bypass graft surgery: a meta-analysis of randomized controlled trials. *J Thorac Cardiovasc Surg*. 2013;146:255–261. doi: 10.1016/j.jtcvs.2012.07.014.
3. Benedetto U, Raja SG, Albanese A, Amrani M, Biondi-Zoccai G, Frati G. Searching for the second best graft for coronary artery bypass surgery: a network meta-analysis of randomized controlled trials. *Eur J Cardiothorac Surg*. 2015;47:59–65. doi: 10.1093/ejcts/ezu111.
4. 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;117:2859–2864. doi: 10.1161/CIRCULATIONAHA.107.736215.
5. Buxton BF, Raman JS, Ruengsakulrach P, Gordon I, Rosalion A, Bellomo R, Horrigan M, Hare DL. Radial artery patency and clinical outcomes: five-year interim results of a randomized trial. *J Thorac Cardiovasc Surg*. 2003;125:1363–1371.
6. Petrovic I, Nezic D, Peric M, Milojevic P, Djokic O, Kosevic D, Tasic N, Djukanovic B, Otasevic P. 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. doi: 10.1186/s13019-015-0331-9.
7. Schwann TA, Tranbaugh RF, Dimitrova KR, Engoren MC, Kabour A, Hoffman DM, Geller CM, Ko W, Habib RH. Time-varying survival benefit of radial artery versus vein grafting: a multiinstitutional analysis. *Ann Thorac Surg*. 2014;97:1328–1334. doi: 10.1016/j.athoracsur.2013.09.096.
8. Hayward PA, Yap CH, Shi WY, Buxton BF, Dinh DT, Reid CM, Shardey GC, Smith JA. Does the addition of a radial artery graft improve survival after higher risk coronary artery bypass grafting? A propensity-score analysis of a multicentre database. *Eur J Cardiothorac Surg*. 2013;44:497–504. doi: 10.1093/ejcts/ezt116.
9. Pullan M, Kirmani BH, Conley T, Oo A, Shaw M, McShane J, Poullis M. The effect of patient sex on survival in patients undergoing isolated coronary artery bypass surgery receiving a radial artery. *Eur J Cardiothorac Surg*. 2015;47:324–330. doi: 10.1093/ejcts/ezu100.
10. Zacharias A, Habib RH, Schwann TA, Riordan CJ, Durham SJ, Shah A. Improved survival with radial artery versus vein conduits in coronary bypass surgery with left internal thoracic artery to left anterior descending artery grafting. *Circulation*. 2004;109:1489–1496. doi: 10.1161/01.CIR.0000121743.10146.78.
11. Benedetto U, Caputo M, Zakkar M, Davies A, Gibbison B, Bryan A, Angelini GD. The effect of obesity on survival in patients undergoing coronary artery bypass graft surgery who receive a radial artery. *Eur J Cardiothorac Surg*. 2017;51:376–381.
12. Di Mauro M, Contini M, Iacò AL, Bivona A, Gagliardi M, Varone E, Bosco P, Calafiore AM. Bilateral internal thoracic artery on the left side: a propensity score-matched study of impact of the third conduit on the right side. *J Thorac Cardiovasc Surg*. 2009;137:869–874. doi: 10.1016/j.jtcvs.2008.09.014.
13. Grau JB, Kuschner CE, Johnson CK, Ferrari G, Zapolanski A, Brizzio ME, Shaw RE. The effects of using a radial artery in patients already receiving bilateral internal mammary arteries during coronary bypass grafting: 30-day outcomes and 14-year survival in a propensity-matched cohort. *Eur J Cardiothorac Surg*. 2016;49:203–210. doi: 10.1093/ejcts/ezv176.
14. Mohammadi S, Dagenais F, Voisine P, Dumont E, Charbonneau E, Marzouk M, Paramythiotis A, Kalavrouziotis D. Impact of the radial artery as an additional arterial conduit during in-situ bilateral internal mammary artery grafting: a propensity score-matched study. *Ann Thorac Surg*. 2016;101:913–918. doi: 10.1016/j.athoracsur.2015.08.054.
15. Shi WY, Tatoulis J, Newcomb AE, Rosalion A, Fuller JA, Buxton BF. Is a third arterial conduit necessary? Comparison of the radial artery and saphenous vein in patients receiving bilateral internal thoracic arteries for triple vessel coronary disease. *Eur J Cardiothorac Surg*. 2016;50:53–60. doi: 10.1093/ejcts/ezv467.
16. Benedetto U, Caputo M, Zakkar M, Bryan A, Angelini GD. Are three arteries better than two? Impact of using the radial artery in addition to bilateral internal thoracic artery grafting on long-term survival. *J Thorac Cardiovasc Surg*. 2016;152:862–869.e2. doi: 10.1016/j.jtcvs.2016.04.054.
17. Taggart DP, Lees B, Gray A, Altman DG, Flather M, Channon K; ART Investigators. Protocol for the Arterial Revascularisation Trial (ART): a randomised trial to compare survival following bilateral versus single internal mammary grafting in coronary revascularisation [ISRCTN46552265]. *Trials*. 2006;7:7. doi: 10.1186/1745-6215-7-7.
18. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York: John Wiley & Sons; 1987.
19. Austin PC. A tutorial and case study in propensity score analysis: an application to estimating the effect of in-hospital smoking cessation counseling on mortality. *Multivariate Behav Res*. 2011;46:119–151. doi: 10.1080/00273171.2011.540480.
20. Cai J, Zhou H, Davis CE. Estimating the mean hazard ratio parameters for clustered survival data with random clusters. *Stat Med*. 1997;16:2009–2020.
21. Goldman S, Sethi GK, Holman W, Thai H, McFalls E, Ward HB, Kelly RF, Rhenman B, Tobler GH, Bakaeen FG, Huh J, Soltero E, Moursi M, Haime M, Crittenden M, Kasirajan V, Ratliff M, Pett S, Irimpen A, Gunnar W, Thomas D, Fremes S, Moritz T, Reda D, Harrison L, Wagner TH, Wang Y, Planting L, Miller M, Rodriguez Y, Juneman E, Morrison D, Pierce MK, Kreamer S, Shih MC, Lee K. Radial artery grafts vs saphenous vein grafts in coronary artery bypass surgery: a randomized trial. *JAMA*. 2011;305:167–174. doi: 10.1001/jama.2010.1976.
22. Nocerino AG, Achenbach S, Taylor AJ. Meta-analysis of effect of single versus dual antiplatelet therapy on early patency of bypass conduits after coronary artery bypass grafting. *Am J Cardiol*. 2013;112:1576–1579. doi: 10.1016/j.amjcard.2013.07.017.
23. Benedetto U, Amrani M, Raja SG; Harefield Cardiac Outcomes Research Group. Guidance for the use of bilateral internal thoracic arteries according to survival benefit across age groups. *J Thorac Cardiovasc Surg*. 2014;148:2706–2711. doi: 10.1016/j.jtcvs.2014.07.088.