

ORIGINAL ARTICLE

Bilateral versus Single Internal-Thoracic-Artery Grafts at 10 Years

David P. Taggart, M.D., Ph.D., Umberto Benedetto, M.D., Ph.D.,
 Stephen Gerry, M.Sc., Douglas G. Altman, D.Sc.,* Alastair M. Gray, Ph.D.,
 Belinda Lees, Ph.D., Mario Gaudino, M.D., Vipin Zamvar, M.S., F.R.C.S.,
 Andrzej Bochenek, M.D., Brian Buxton, M.D., Cliff Choong, M.D.,
 Stephen Clark, M.D., Marek Deja, M.D., Jatin Desai, M.D., Ragheb Hasan, M.D.,
 Marek Jasinski, M.D., Peter O'Keefe, M.D., Fernando Moraes, M.D.,
 John Pepper, M.D., Siven Seevanayagam, M.D., Catherine Sudarshan, M.D.,
 Uday Trivedi, M.D., Stanislaw Wos, M.D., John Puskas, M.D., and
 Marcus Flather, M.B., B.S., for the Arterial Revascularization Trial Investigators†

ABSTRACT

BACKGROUND

Multiple arterial grafts may result in longer survival than single arterial grafts after coronary-artery bypass grafting (CABG) surgery. We evaluated the use of bilateral internal-thoracic-artery grafts for CABG.

METHODS

We randomly assigned patients scheduled for CABG to undergo bilateral or single internal-thoracic-artery grafting. Additional arterial or vein grafts were used as indicated. The primary outcome was death from any cause at 10 years. The composite of death from any cause, myocardial infarction, or stroke was a secondary outcome.

RESULTS

A total of 1548 patients were randomly assigned to undergo bilateral internal-thoracic-artery grafting (the bilateral-graft group) and 1554 to undergo single internal-thoracic-artery grafting (the single-graft group). In the bilateral-graft group, 13.9% of the patients received only a single internal-thoracic-artery graft, and in the single-graft group, 21.8% of the patients also received a radial-artery graft. Vital status was not known for 2.3% of the patients at 10 years. In the intention-to-treat analysis at 10 years, there were 315 deaths (20.3% of the patients) in the bilateral-graft group and 329 deaths (21.2%) in the single-graft group (hazard ratio, 0.96; 95% confidence interval [CI], 0.82 to 1.12; $P=0.62$). Regarding the composite outcome of death, myocardial infarction, or stroke, there were 385 patients (24.9%) with an event in the bilateral-graft group and 425 patients (27.3%) with an event in the single-graft group (hazard ratio, 0.90; 95% CI, 0.79 to 1.03).

CONCLUSIONS

Among patients who were scheduled for CABG and had been randomly assigned to undergo bilateral or single internal-thoracic-artery grafting, there was no significant between-group difference in the rate of death from any cause at 10 years in the intention-to-treat analysis. Further studies are needed to determine whether multiple arterial grafts provide better outcomes than a single internal-thoracic-artery graft. (Funded by the British Heart Foundation and others; Current Controlled Trials number, ISRCTN46552265.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Flather at Norwich Medical School, University of East Anglia, Norwich NR4 7TJ, United Kingdom, or at m.flather@uea.ac.uk.

*Deceased.

†A complete list of the investigators in the Arterial Revascularization Trial is provided in the Supplementary Appendix, available at NEJM.org.

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CORONARY-ARTERY BYPASS GRAFTING (CABG) surgery with the use of left internal-thoracic-artery grafts plus vein grafts is an effective way to treat patients with symptomatic advanced coronary artery disease^{1,2} and has been shown to be superior to percutaneous coronary intervention in patients with severe coronary artery disease and in those with diabetes.³ The benefit of using left internal-thoracic-artery grafts has been well established, and this benefit has been attributed to their superior long-term patency as compared with vein grafts.⁴⁻⁷

Pooled observational studies have shown lower long-term mortality when both left and right internal-thoracic-artery grafts are used for CABG than when a single internal-thoracic-artery graft is used.^{8,9} This finding has been attributed to the excellent long-term angiographic patency of the right internal-thoracic-artery graft, which appears to be similar to that of the left.^{10,11} It is hypothesized that routine use of the right internal thoracic artery for grafting in addition to the left would provide better clinical outcomes because of improved long-term graft patency.¹²

In the Arterial Revascularization Trial (ART), we randomly assigned patients to receive either bilateral internal-thoracic-artery grafts or a standard single left internal-thoracic-artery graft during CABG. A prespecified interim analysis at 5 years showed no significant differences between the two strategies with regard to all-cause mortality or the rate of the composite outcome of death from any cause, myocardial infarction, or stroke.¹³ The current report presents the primary analysis at 10 years of follow-up.

METHODS

TRIAL DESIGN

We conducted this two-group, multicenter, randomized, unblinded trial at 28 hospitals in seven countries (Australia, Austria, Brazil, India, Italy, Poland, and the United Kingdom). The protocol (available with the full text of this article at NEJM.org), baseline data, 1-year safety outcomes, and the prespecified interim analysis at 5 years have been published previously.¹²⁻¹⁴ The trial complied with the principles of the Declaration of Helsinki and commenced after ethics approval was obtained at all the participating centers. The trial was managed by the University of Oxford

and was funded by the British Heart Foundation, the U.K. Medical Research Council, and the National Institute of Health Research Efficacy and Mechanistic Evaluation Program. The managing institution and the funders had no role in the design or conduct of the trial, in the analysis of the data, or in the writing of the manuscript or the decision to submit it for publication.

Trial coordination was provided initially by the Clinical Trials and Evaluation Unit at the Royal Brompton and Harefield NHS Foundation Trust in London and from 2014 by the Surgical Intervention Trials Unit at the University of Oxford. The authors were responsible for the design and analysis of the trial and take full responsibility for the integrity and completeness of the data and for the contents of the article, as well as for the fidelity of the trial to the protocol.

ENROLLMENT AND RANDOMIZATION OF THE PATIENTS

Eligible patients were those with multivessel coronary artery disease who were scheduled to undergo CABG (including patients for whom urgent surgery was indicated, but not those with evolving myocardial infarction). Patients for whom only single grafts or concomitant valve surgery was planned, as well as those with a history of CABG, were excluded. Each patient was required to provide written informed consent.

Patients were randomly assigned, in a 1:1 ratio, to undergo bilateral or single internal-thoracic-artery grafting. Randomization was performed by means of a telephone call to the coordinating center. The randomization sequence was generated with randomly varying block sizes and stratified according to center. To reduce the possibility of outcome events occurring between randomization and revascularization, it was recommended that surgery be performed within 6 weeks after randomization.

SURGICAL PROCEDURE

The bilateral internal-thoracic-artery grafting group (henceforth, the bilateral-graft group) received both left and right internal-thoracic-artery grafts to the two most important coronary arteries on the left side, with supplemental vein grafts or radial-artery grafts to other coronary arteries as clinically indicated. In the bilateral-graft group, internal-thoracic-artery grafts could be used as

composite grafts to each other, as long as one remained in situ. Anastomosis of an internal-thoracic-artery graft to the right coronary artery was not permitted because of concerns about inferior long-term patency. The single internal-thoracic-artery grafting group (henceforth, the single-graft group) received a single internal-thoracic-artery graft to the left anterior descending coronary artery plus supplemental vein grafts or radial-artery grafts to other coronary arteries as determined by the responsible cardiac surgeon.

Surgeons could participate in the trial only if their experience included 50 or more operations using bilateral internal-thoracic-artery grafts, and surgeons were expected to be able to perform either procedure. Standard methods for anesthesia and myocardial protection were used according to local practice, and participating centers were encouraged to provide evidence-based preventive medical treatments.

OUTCOME MEASURES

The primary outcome was death from any cause at 10 years of follow-up. Secondary outcomes were the composite of death from any cause, myocardial infarction, or stroke (in a time-to-event analysis), rate of repeat revascularization, and safety outcomes (including bleeding and sternal wound complications). Information on quality of life, costs, and cost effectiveness was also collected and is reported separately.¹⁵ Outcome definitions are provided in the Supplementary Appendix, available at NEJM.org.

Data were gathered at participating sites by means of annual telephone calls or hospital visits. Participating centers were encouraged to obtain vital-status data by means of contact with family doctors and central registers where available. Serious adverse events were reported by investigators on specific forms. All the outcome events, including adverse events, underwent adjudication as described in the Supplementary Appendix.¹²

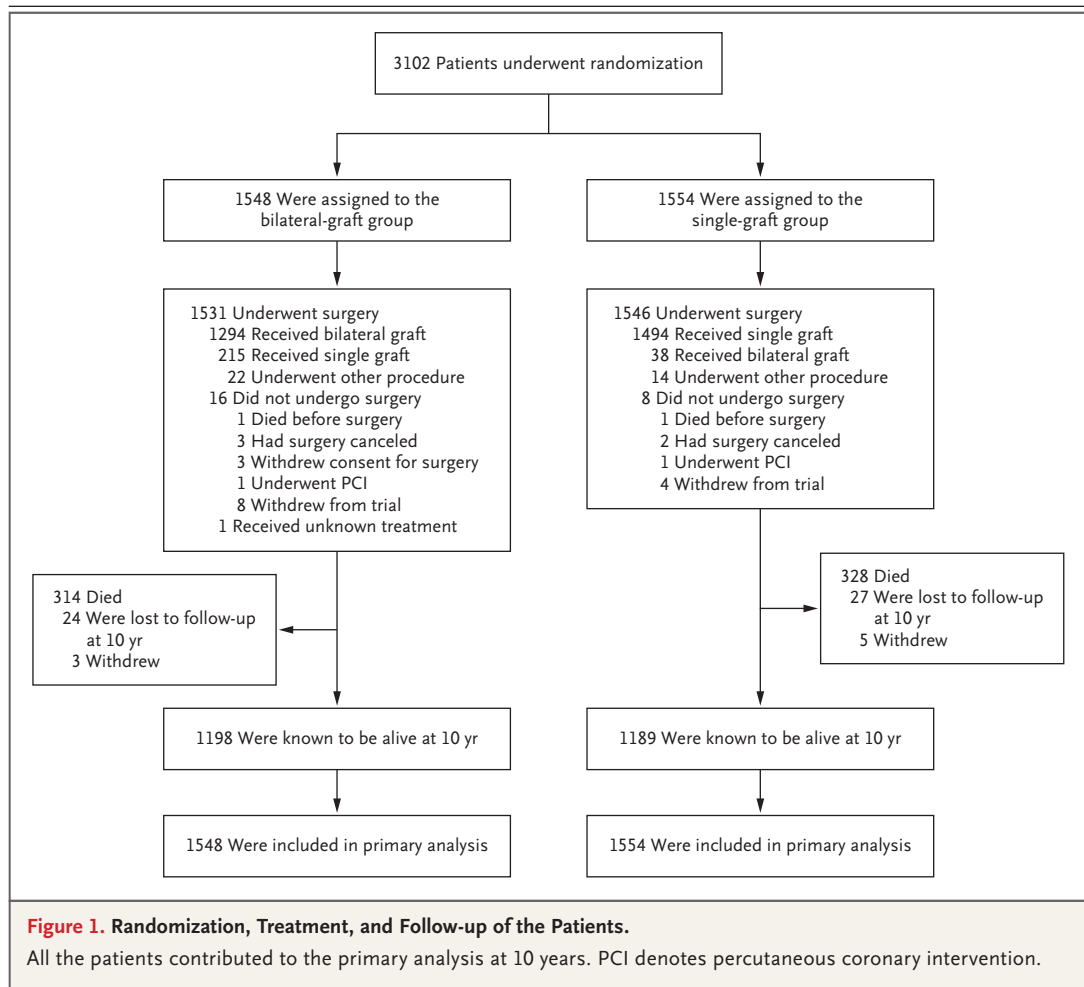
STATISTICAL ANALYSIS

On the basis of a previous systematic review,⁸ we estimated that the use of bilateral internal-thoracic-artery grafting would result in all-cause mortality at 10 years that was 5 percentage points lower than mortality with single internal-thoracic-artery grafting (20% vs. 25%). We calculated that 2928 patients would need to be en-

rolled in order for the trial to detect this expected difference with 90% power at the 5% significance level. The aim was to enroll 3000 patients (1500 in each group) over a recruitment period of 2 to 3 years and to follow them for 10 years.

This analysis censored data from the patients at 10 years of follow-up after the date of randomization. The primary analysis used the intention-to-treat principle. A sensitivity analysis was carried out with adjustment for age (<70 years vs. ≥70 years), sex, ejection fraction (≤50% vs. >50%), and diabetes (yes vs. no). The time-to-event analysis of survival was performed with the use of the log-rank method and Cox proportional-hazards regression to estimate hazard ratios and 95% confidence intervals. For patients who died on their date of randomization or for whom their last known follow-up occurred on that day, their survival time was assumed to be half a day, in order to allow them to be included in the analysis. A competing-risks analysis was used in the analyses of myocardial infarction, stroke, and cause-specific mortality.

Prespecified subgroup analyses were performed on the basis of baseline diagnosis of diabetes (yes vs. no), age (<70 years vs. ≥70 years), type of surgery (on pump vs. off pump), radial-artery grafting (yes vs. no), number of grafts (≤3 vs. >3), and ejection fraction (≤50% vs. >50%). Prespecified exploratory analyses for the primary outcome included a per-protocol analysis (which included only patients who actually received their randomly assigned treatment) and an as-treated analysis in which we compared patients who received at least two arterial grafts (left internal-thoracic-artery graft plus a right internal-thoracic-artery graft, a radial-artery graft, or both) with those who received a single arterial graft that used only the left internal thoracic artery for grafting, with multivariable adjustment for imbalances in baseline characteristics. A P value of less than 0.05 was considered to indicate statistical significance for the primary outcome. All the other outcomes are summarized with hazard ratios and confidence intervals for clinical outcomes and with relative risks and confidence intervals for adverse events. Confidence intervals have not been adjusted for multiple comparisons and therefore should not be used to infer definitive treatment effects. All the analyses were



performed with the use of Stata software, version 14 (StataCorp).

RESULTS

PATIENTS

From June 2004 through December 2007, we enrolled 3102 patients in the trial. A total of 1548 patients were randomly assigned to the bilateral-graft group and 1554 patients to the single-graft group. Figure 1 shows the flow of the patients through the trial up to 10 years of follow-up. One patient in each group died before undergoing surgery. Information on vital status (dead or alive) was missing at the final 10-year follow-up for 71 patients (2.3%), and 279 patients (9.0%) had incomplete data over the course of the trial regarding myocardial infarction, stroke, and repeat revascularization. The groups were well matched with respect to age, sex, race, body-mass index,

systolic and diastolic blood pressure, smoking status, and coexisting conditions (Table 1, and Table S1 in the Supplementary Appendix).

TREATMENT

Data on surgical details, postoperative care, and length of stay in the hospital are provided in Table S2 in the Supplementary Appendix.¹⁴ In the bilateral-graft group, 83.6% of the patients received bilateral internal-thoracic-artery grafts (13.9% of the patients received only a single internal-thoracic-artery graft), and in the single-graft group, 96.1% of the patients received a single internal-thoracic-artery graft. A large variation, from 0 to 100%, was observed among surgeons in rates of conversion from a planned bilateral internal-thoracic-artery graft procedure to an unplanned single internal-thoracic-artery graft procedure, with generally lower rates of crossover among surgeons who performed more

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Bilateral-Graft Group (N=1548)	Single-Graft Group (N=1554)
Age at randomization — yr	63.7±8.7	63.5±9.1
Male sex — no. (%)	1318 (85.1)	1338 (86.1)
Smoking status — no. (%)		
Current smoking	237 (15.3)	214 (13.8)
Former smoking	834 (53.9)	898 (57.8)
Never smoked	477 (30.8)	442 (28.4)
Race — no. (%)†		
White	1418 (91.6)	1431 (92.1)
Other	130 (8.4)	122 (7.9)
Missing data	0	1 (0.1)
Height — cm	170.0±8.5	170.4±8.4
Weight — kg	82.0±13.5	81.9±14.2
Body-mass index	28.3±4.0	28.1±4.1
Systolic blood pressure — mm Hg	131.7±18.0	131.8±18.5
Diastolic blood pressure — mm Hg	75.0±11.0	74.8±11.1
Diabetes — no. (%)		
No history	1177 (76.0)	1191 (76.6)
Insulin-dependent diabetes	95 (6.1)	79 (5.1)
Non–insulin-dependent diabetes	276 (17.8)	284 (18.3)
Hypertension treated with drugs — no. (%)	1193 (77.1)	1217 (78.3)
Hyperlipidemia treated with drugs — no./total no. (%)	1457/1547 (94.2)	1448/1554 (93.2)
Documented peripheral arterial disease — no. (%)	103 (6.7)	118 (7.6)
Documented transient ischemic attack — no./total no. (%)	53/1548 (3.4)	57/1553 (3.7)
Previous stroke — no./total no. (%)	42/1548 (2.7)	48/1553 (3.1)
Previous myocardial infarction — no./total no. (%)	619/1547 (40.0)	681/1553 (43.9)
Previous PCI, with or without stent — no./total no. (%)	242/1547 (15.6)	248/1553 (16.0)

* Plus–minus values are means ±SD. Data were missing as follows: height and body-mass index (the weight in kilograms divided by the square of the height in meters), for six patients in the bilateral-graft group and for two in the single-graft group; weight, for two in the bilateral-graft group; and blood pressure, for three in the bilateral-graft group and one in the single-graft group. Percentages may not total 100 because of rounding. PCI denotes percutaneous coronary intervention.

† Race was reported by the patient.

than 50 operations in the trial (Fig. S1 in the Supplementary Appendix). Approximately 40% of the procedures in each group were performed off pump without the use of cardiopulmonary bypass, and the mean number of grafts in each group was 3 (Table S2 in the Supplementary Appendix). Additional radial-artery grafts were used in 19.4% of the patients in the bilateral-graft group and in 21.8% of those in the single-graft group. Medications at 10 years were well balanced between the two groups, with aspirin

used in an average of 81.0% of the patients, beta-blockers in 73.8%, statins in 90.4%, and angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers in 72.5% (Table S3 in the Supplementary Appendix).

OUTCOMES

A total of 644 patients (20.8% of the overall trial population) had died by 10 years, with 315 deaths (20.3%) occurring in the bilateral-graft group and 329 (21.2%) in the single-graft group

Table 2. Clinical Outcomes and Adverse Events at 10 Years (Intention-to-Treat Analysis).

Variable	Bilateral-Graft Group (N = 1548)	Single-Graft Group (N = 1554)	Hazard Ratio or Relative Risk (95% CI)*	P Value
	<i>number (percent)</i>			
Clinical outcome				
Primary outcome: death from any cause	315 (20.3)	329 (21.2)	0.96 (0.82–1.12)	0.62
Composite of death, myocardial infarction, or stroke	385 (24.9)	425 (27.3)	0.90 (0.79–1.03)	—
Myocardial infarction†	71 (4.6)	78 (5.0)	0.92 (0.66–1.26)	—
Stroke†	57 (3.7)	76 (4.9)	0.75 (0.53–1.06)	—
Adverse event				
Repeat revascularization	159 (10.3)	156 (10.0)	1.02 (0.83–1.26)	—
Major bleeding‡	52 (3.4)	48 (3.1)	1.09 (0.74–1.61)	—
Sternal wound complication‡	54 (3.5)	30 (1.9)	1.81 (1.16–2.81)	—
Sternal wound reconstruction‡	31 (2.0)	10 (0.6)	3.11 (1.53–6.32)	—

* Hazard ratios (for clinical outcomes) and relative risks (for adverse events) use the single-graft group as the reference. The confidence intervals that are reported in this table have not been adjusted for multiple testing and therefore should not be used to infer definitive treatment effects.

† These rows include all the patients with myocardial infarction or stroke up to 10 years and not just those that form part of the composite. Since death is a competing risk for myocardial infarction and for stroke, the analysis takes account of this, and therefore the hazard ratio refers to the subhazard ratio for these two rows.

‡ These events relate to the period from the trial-related surgical procedure to 6 months of follow-up.

(hazard ratio, 0.96; 95% confidence interval [CI], 0.82 to 1.12; $P=0.62$) (Table 2 and Fig. 2A). Results were similar after adjustment for age, sex, diabetes status, and ejection fraction (hazard ratio, 0.97; 95% CI, 0.83 to 1.14). Approximately half the deaths were classified as being of non-cardiovascular cause (Table S4 in the Supplementary Appendix).

Regarding the composite outcome of death from any cause, myocardial infarction, or stroke, there were 385 patients (24.9%) with an event in the bilateral-graft group and 425 (27.3%) with an event in the single-graft group (hazard ratio, 0.90; 95% CI, 0.79 to 1.03) (Table 2 and Fig. 2B). Results of the individual components of this outcome are shown in Table 2; there were no significant differences between the two groups.

There was no significant between-group difference in the rate of repeat revascularization (10.3% in the bilateral-graft group and 10.0% in the single-graft group) (Table 2). There were no significant differences in the rate of early major bleeding events. Sternal wound complications during the first 6 months of follow-up occurred in 54 patients (3.5%) in the bilateral-graft group and in 30 (1.9%) in the single-graft group (relative risk, 1.81; 95% CI, 1.16 to 2.81). Intention-

to-treat analyses of the primary outcome according to subgroups did not show any evidence of significant interactions (Fig. 3).

The per-protocol analysis included only patients who underwent surgery according to their randomized assignment. The results regarding the primary outcome in the per-protocol analysis were similar to those in the intention-to-treat analysis (Table S5 in the Supplementary Appendix).

The as-treated analysis compared patients who received multiple arterial grafts with those who received a single arterial graft, regardless of randomization assignment. In the as-treated analysis, patients in the single-graft group who also received a radial-artery graft were included in the multiple-graft group. The characteristics of the patients at baseline in the as-treated analysis are shown in Table S6 in the Supplementary Appendix.

In the as-treated analysis, there were 315 deaths among 1690 patients (18.6%) in the group with two or more arterial grafts and 307 deaths among 1330 patients (23.1%) in the group with a single internal-thoracic-artery graft (adjusted hazard ratio, 0.81; 95% CI, 0.68 to 0.95). The composite outcome of death, myocardial infarction, or stroke occurred in 399 patients (23.6%)

in the group with two or more arterial grafts and in 385 patients (28.9%) in the group with a single internal-thoracic-artery graft (adjusted hazard ratio, 0.80; 95% CI, 0.69 to 0.93). Details are provided in Figure S2 and Table S7 in the Supplementary Appendix.

DISCUSSION

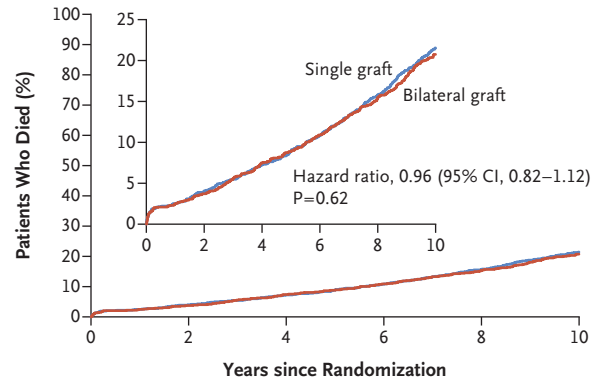
ART was a randomized trial that compared bilateral with single internal-thoracic-artery grafting for CABG. At 10 years, in intention-to-treat analyses, there were no significant between-group differences in all-cause mortality; in the rate of the composite outcome of death, myocardial infarction, or stroke; or in the rate of repeat revascularization.

The results of this trial are not consistent with data from previous, nonrandomized studies. Potential benefits of use of the second internal thoracic artery for grafting were suggested by a combination of reported reductions in mortality in observational studies^{8,9} and strong evidence of superior rates of angiographic patency of both left and right internal-thoracic-artery grafts as compared with saphenous-vein grafts.^{6,11}

There are several possible reasons for the lack of evidence of benefit of bilateral internal-thoracic-artery grafts as compared with single internal-thoracic-artery grafts in ART. First, although vein-graft failure is a common finding in patients after CABG surgery (up to 50% within 10 years), there is conflicting evidence about its clinical effect on survival.^{6,16} However, there is also robust evidence that complete rather than incomplete revascularization has an important survival advantage,¹⁷ which seems intuitively consistent with the concept that having more patent grafts at 10 years would prolong survival.

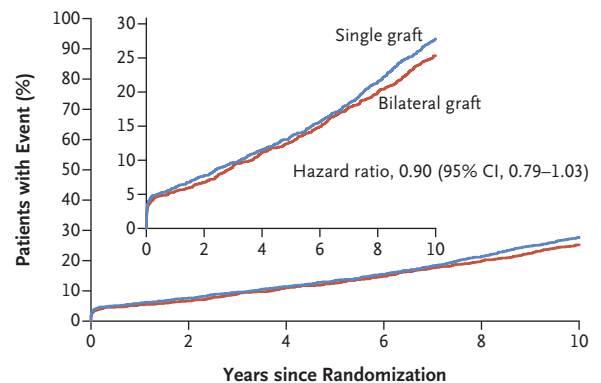
Second, 14% of the patients who had been randomly assigned to the bilateral-graft group actually underwent single internal-thoracic-artery grafting, and 22% of those who had been randomly assigned to the single-graft group also received a second arterial graft in the form of a radial-artery graft. When ART was designed in 2001, it was not known that radial-artery grafts would provide additional clinical benefits as compared with saphenous-vein grafts. Since then, there has been growing evidence of the superior angiographic patency of radial-artery grafts as compared with saphenous-vein grafts,^{18,19} which

A Death from Any Cause at 10 Yr



No. at Risk						
Single graft	1554	1484	1432	1370	1283	894
Bilateral graft	1548	1481	1417	1359	1283	882

B Composite of Death from Any Cause, Myocardial Infarction, or Stroke at 10 Yr



No. at Risk						
Single graft	1554	1427	1366	1296	1195	820
Bilateral graft	1548	1435	1362	1299	1214	830

Figure 2. Primary Outcome of Death from Any Cause and Composite Outcome of Death from Any Cause, Myocardial Infarction, or Stroke at 10 Years.

Hazard ratios use the single-graft group as the reference. Insets show the same data on an enlarged y axis.

has resulted in better clinical outcomes. An individual patient-level pooled analysis of six randomized trials has shown that the use of radial-artery grafts was associated with superior angiographic patency and better clinical outcomes than the use of vein grafts at 5 years of follow-up.¹⁸

Consequently, the use of radial-artery grafts in ART may be a key confounder, because it is likely to preferentially benefit the single-graft group by the addition of an arterial graft to the second most important coronary artery. When data from patients were analyzed according to

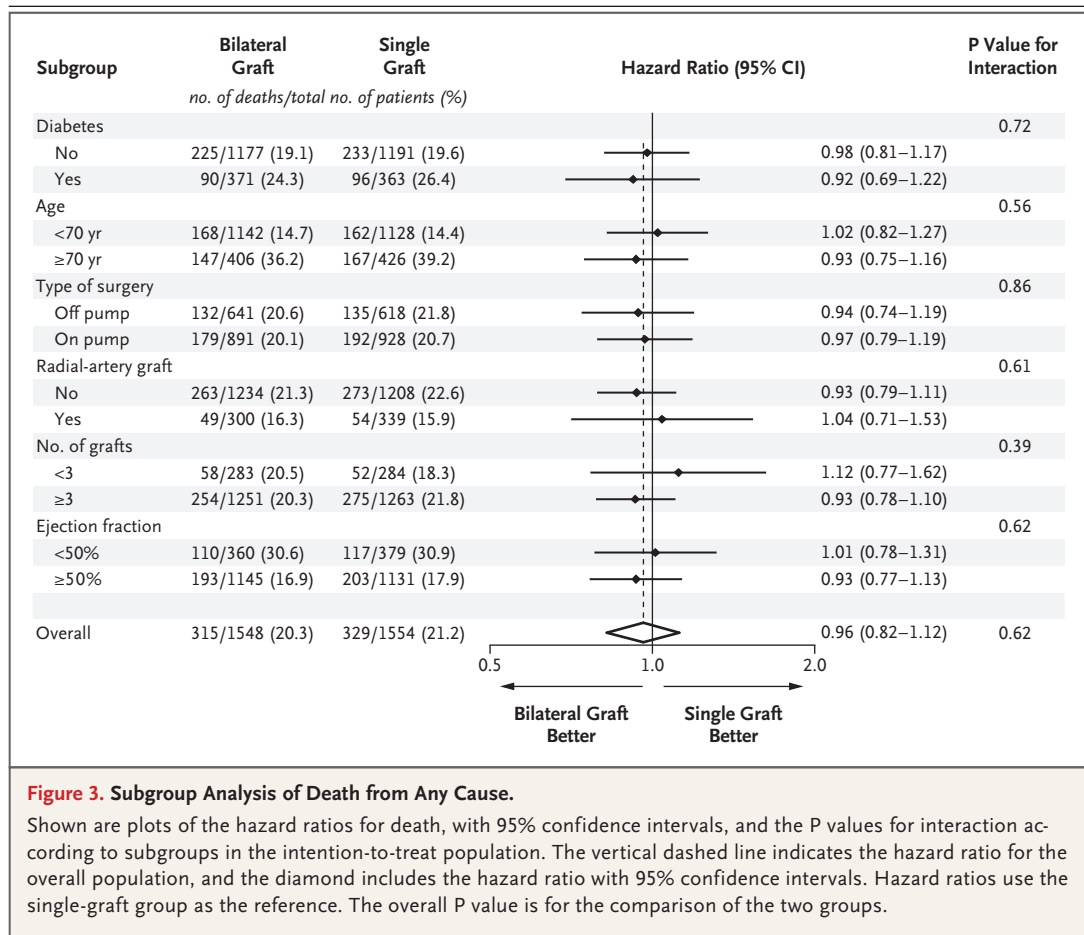


Figure 3. Subgroup Analysis of Death from Any Cause.

Shown are plots of the hazard ratios for death, with 95% confidence intervals, and the P values for interaction according to subgroups in the intention-to-treat population. The vertical dashed line indicates the hazard ratio for the overall population, and the diamond includes the hazard ratio with 95% confidence intervals. Hazard ratios use the single-graft group as the reference. The overall P value is for the comparison of the two groups.

the actual receipt of two or more arterial grafts, as compared with a single arterial graft (the as-treated analysis), there appeared to be a meaningful difference in mortality in favor of multiple arterial grafts — a finding that is consistent with growing evidence of the benefits of multiple arterial grafting.²⁰ However, this comparison was not based on randomization assignment, and although the patients in these two groups in the as-treated analysis were well matched with regard to baseline clinical characteristics, extent of coronary artery disease, and number of grafts, it will be useful to test the benefit of multiple arterial grafts in a randomized trial. This question is currently being addressed in the Randomized Comparison of the Clinical Outcome of Single versus Multiple Arterial Grafts (ROMA) trial.²¹

Third, 14% of the patients who had been assigned to the bilateral-graft group actually received a single internal-thoracic-artery graft, which may

have influenced the relative effectiveness of bilateral internal-thoracic-artery grafting.^{22–25} This crossover rate was considerably higher than expected, with wide variation (from 0% to 100%) among surgeons, but the surgeons who performed more operations in the trial appeared to have lower crossover rates.²⁴ Substantial rates of nonadherence to the randomly assigned treatment result in a loss of statistical power. In addition, intraoperative conversions to the other procedure in ART also resulted in higher rates of adverse clinical events at 5 years than did receipt of the randomly assigned procedure,²⁴ which would tend to favor the single-graft group. The effect of the surgeon's experience on outcomes after bilateral internal-thoracic-artery graft surgery is increasingly recognized.^{26,27}

Fourth, adherence to guideline-directed medical therapy in patients undergoing CABG is increasingly recognized as a major determinant of

clinical outcome, including survival.²⁸ The exceptionally high rate of guideline-directed medical therapy in ART (Table S3 in the Supplementary Appendix), as compared with other contemporary trials of stents versus CABG,²⁸ may have served to narrow differences in the clinical outcome rates between the two groups.

There are several other potential limitations to be considered. ART was an unblinded trial in which the treatment-group assignment was known to the patients, investigators, and care providers, and as a result, biases may be introduced in the treatment of patients, depending on their randomization assignment. Important center-, surgeon-, and patient-driven effects may not be fully accounted for, and the generalizability of surgical trials may be more difficult to ensure than the generalizability of trials of medication-based therapies.²⁹ No follow-up angiograms or studies of myocardial viability were carried out, which limits the consideration of graft patency and patterns of ischemia.

In conclusion, ART was a randomized trial of bilateral internal-thoracic-artery grafting, as compared with single internal-thoracic-artery grafting, in patients undergoing CABG. In the intention-to-treat analysis, we found no significant differences between the two groups in the rate of death from any cause or the rate of the com-

posite outcome of death, myocardial infarction, or stroke.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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No potential conflict of interest relevant to this article was reported.

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

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This article is dedicated to the memory of Dr. Douglas G. Altman, who inspired us all in this trial and who died on June 3, 2018.

APPENDIX

The authors' affiliations are as follows: the Nuffield Department of Surgical Sciences, John Radcliffe Hospital (D.P.T., B.L.), the Centre for Statistics in Medicine, Botnar Research Centre (S.G., D.G.A.), and the Health Economics Research Centre, Nuffield Department of Population Health (A.M.G.), University of Oxford, Oxford, the School of Clinical Sciences, University of Bristol, and Bristol Royal Infirmary, Bristol (U.B.), the Department of Cardiac Surgery, Royal Infirmary of Edinburgh, Edinburgh (V.Z.), Royal Papworth Hospital, Cambridge (C.C., C.S.), the Department of Cardiac Surgery, Freeman Hospital, Newcastle (S.C.), the Department of Cardiac Surgery, King's College Hospital (J.D.), and Royal Brompton Hospital and Imperial College London (J. Pepper), London, the Department of Cardiac Surgery, Royal Infirmary, Manchester (R.H.), the Department of Cardiac Surgery, University Hospital of Wales, Cardiff (P.O.), the Department of Cardiac Surgery, Royal Sussex County, Brighton (U.T.), and Norwich Medical School, University of East Anglia, and Norfolk and Norwich University Hospital, Norwich (M.F.) — all in the United Kingdom; the Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York Presbyterian Hospital (M.G.), and Mount Sinai St. Luke's (J. Puskas) — both in New York; the Center for Cardiovascular Research and Development, American Heart of Poland (A.B.), and the Department of Cardiac Surgery, Medical University of Silesia (M.D., S.W.), Katowice, and the Department of Cardiac and Thoracic Surgery, Wroclaw Medical University, Wroclaw (M.J.) — all in Poland; the Department of Cardiac Surgery, Austin Health, Melbourne, VIC, Australia (B.B., S.S.); and the Heart Institute of Pernambuco, Recife, Brazil (F.M.).

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