ORIGINAL ARTICLE

Randomized Trial of Bilateral versus Single Internal-Thoracic-Artery Grafts

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ABSTRACT

BACKGROUND

The use of bilateral internal thoracic (mammary) arteries for coronary-artery bypass grafting (CABG) may improve long-term outcomes as compared with the use of a single internal-thoracic-artery plus vein grafts.

METHODS

We randomly assigned patients scheduled for CABG to undergo single or bilateral internal-thoracic-artery grafting in 28 cardiac surgical centers in seven countries. 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. Interim analyses were prespecified at 5 years of follow-up.

RESULTS

A total of 3102 patients were enrolled; 1554 were randomly assigned to undergo single internal-thoracic-artery grafting (the single-graft group) and 1548 to undergo bilateral internal-thoracic-artery grafting (the bilateral-graft group). At 5 years of follow-up, the rate of death was 8.7% in the bilateral-graft group and 8.4% in the single-graft group (hazard ratio, 1.04; 95% confidence interval [CI], 0.81 to 1.32; P=0.77), and the rate of the composite of death from any cause, myocardial infarction, or stroke was 12.2% and 12.7%, respectively (hazard ratio, 0.96; 95% CI, 0.79 to 1.17; P=0.69). The rate of sternal wound complication was 3.5% in the bilateral-graft group versus 1.9% in the single-graft group (P=0.005), and the rate of sternal reconstruction was 1.9% versus 0.6% (P=0.002).

CONCLUSIONS

Among patients undergoing CABG, there was no significant difference between those receiving single internal-thoracic-artery grafts and those receiving bilateral internal-thoracic-artery grafts with regard to mortality or the rates of cardiovascular events at 5 years of follow-up. There were more sternal wound complications with bilateral internal-thoracic-artery grafting than with single internal-thoracic-artery grafting. Ten-year follow-up is ongoing. (Funded by the British Heart Foundation and others; ART Current Controlled Trials number, ISRCTN46552265.)

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*A complete list of investigators and participating centers in the Arterial Revascularization Trial (ART) is provided in the Supplementary Appendix, available at NEJM.org.

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Coronary-artery bypass grafting (CABG) is one of the most commonly performed operations worldwide and has been established as an effective treatment for symptomatic multivessel coronary artery disease.[1,2] The standard surgical approach is anastomosis of the left internal thoracic (mammary) artery to the left anterior descending coronary artery and the use of saphenous-vein or radial-artery grafts to bypass other coronary arteries.[3,4] The single internal-thoracic-artery graft has a 10-year rate of angiographic patency exceeding 90%, as compared with 50% for vein grafts.[5-10]

The excellent long-term outcomes of single internal-thoracic-artery grafts[11,12] have stimulated the use of a bilateral internal-thoracic-artery approach that uses both the left and right internal thoracic arteries.[13-16] Pooled analyses of observational studies suggest that, at 10 years, there are approximately 20% fewer deaths from any cause with bilateral internal-thoracic-artery grafting than with single internal-thoracic-artery grafting.[17-21] However, bilateral internal-thoracic-artery grafting has not been widely adopted because of three main factors: it is a more complex procedure, it is associated with a higher risk of sternal wound complications, and there is a lack of randomized evidence of benefit.[22-24]

The Arterial Revascularization Trial (ART) was initiated in 2004 to address these concerns.[25] The primary objective of the trial was to compare 10-year survival rates associated with bilateral and single internal-thoracic-artery grafting, and secondary outcomes included clinical events, quality of life, and health economic measures. Safety information at 1 year has been published previously,[26] and the current report is an interim analysis of clinical and safety outcomes at 5 years.

Methods

Trial Design

This two-group, multicenter, randomized trial was conducted in 28 cardiac surgical centers in seven countries. The protocol (available with the full text of this article at NEJM.org), baseline data, and 1-year safety outcomes have been published previously.[25,26] The trial complies with the Declaration of Helsinki and commenced after ethics approval was obtained at all the participating centers. The trial was sponsored by the University of Oxford, with funding from the British Heart Foundation, the U.K. Medical Research Council, and the National Institute of Health Research Efficacy and Mechanism Evaluation Programme. 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. There was no support from commercial entities for this trial.

Trial management 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 study 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 this report to the trial protocol.

Enrollment and Randomization of the Patients

Eligible patients were those with multivessel coronary artery disease who were scheduled to undergo CABG (including patients requiring urgent surgery, but not those with evolving myocardial infarction). Patients requiring only single grafts or concomitant valve surgery, 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 single or bilateral internal-thoracic-artery grafting. The randomization sequence was generated with randomly varying block sizes and stratified according to center. Patients were enrolled and underwent randomization by means of a telephone call to the coordinating 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 group that underwent single internal-thoracic-artery grafting (the single-graft group) received a single internal-thoracic-artery graft to the left anterior descending coronary artery plus supplemental vein or radial-artery grafts to other coronary arteries. The group that underwent bilateral internal-thoracic-artery grafting (the bilateral-graft

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group) received both left and right internal-thoracic-artery grafts to the two most important coronary arteries on the left side with supplemental vein or radial-artery grafts to other coronary arteries. 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.

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.

OUTCOME MEASURES

The primary outcome of the trial 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, safety outcomes (including bleeding and sternal wound complications), quality of life, costs, and cost effectiveness. Outcome definitions are provided in the Supplementary Appendix, available at NEJM.org. An analysis at 5 years of follow-up was prespecified by the steering committee and endorsed by the data and safety monitoring committee.[25]

Data were gathered at participating sites by means of annual telephone calls or hospital visits. Serious adverse events were reported by investigators on specific forms. Two members of the clinical-event review committee (see the Supplementary Appendix for the membership list) adjudicated each event (death, myocardial infarction, stroke, and reintervention) in a blinded fashion to ensure that events met the prespecified protocol definitions.[25] If the two adjudicators did not concur, then the event was adjudicated by a third person to reach resolution. All other adverse events that required or prolonged hospitalization were adjudicated by one member of the committee. Quality of life was assessed with the use of the shortened World Health Organization (WHO) Rose angina questionnaire,[27] the European Quality of Life–5 Dimensions (EQ-5D) questionnaire,[28] and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).[29]

STATISTICAL ANALYSIS

On the basis of a previous systematic review,[17] we estimated that the use of bilateral internal-thoracic-artery grafting would result in 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 enrolled in order for the trial to detect this expected difference with 90% power at the 5% significance level. The aim was to enroll at least 3000 patients (1500 patients in each group) over a recruitment period of 2 to 3 years.

This analysis censored data from patients at 5 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. All hazard ratios were estimated with the single internal-thoracic-artery group as the control group. For patients who died on their date of randomization or for whom their last known follow-up occurred on that day, their survival duration 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), surgery type (on pump vs. off pump), radial-artery grafting (yes vs. no), number of grafts (<3 vs. ≥3), and ejection fraction (<50% vs. ≥50%). Exploratory analyses for the primary outcome included a per-protocol analysis (which included patients who actually received their randomly assigned treatment) and an as-treated analysis (in which patients were compared on the basis of the treatment they actually received). Health-related quality-of-life results are presented as percentages and means as appropriate; only patients with data are included in these analyses, without imputation for missing data, which is planned for only the

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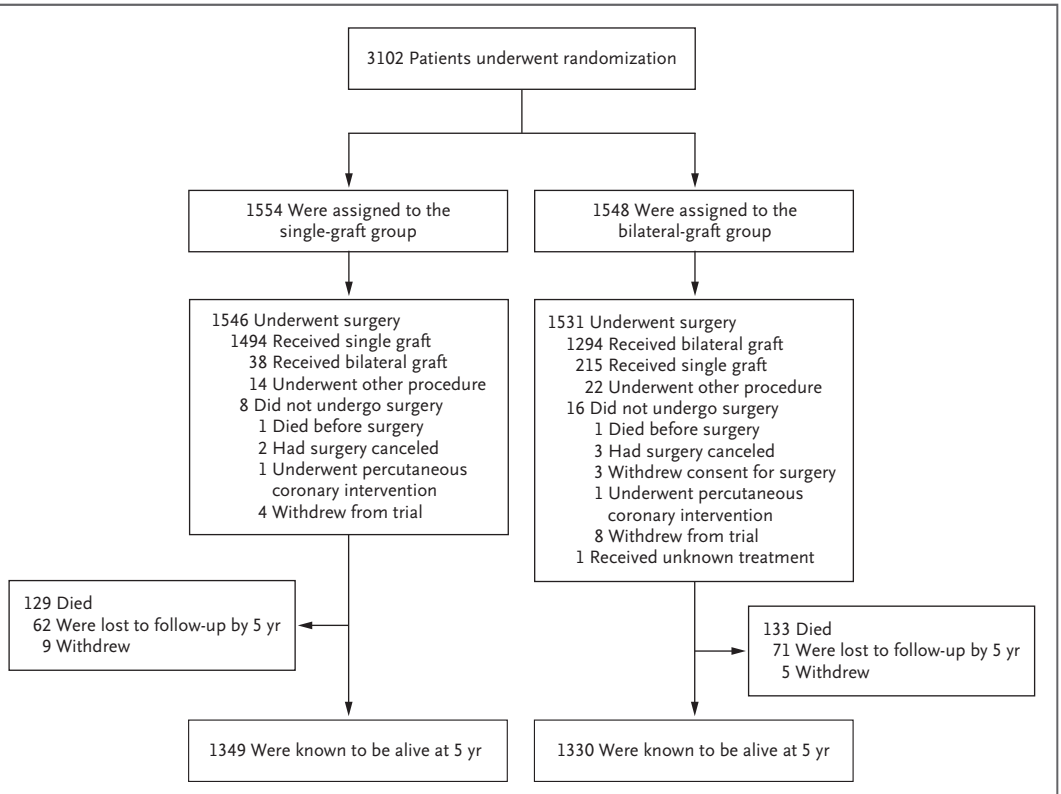

Figure 1. Randomization, Enrollment, and Follow-up of the Patients.

The number of patients who underwent randomization in each group can be derived by adding the numbers of patients who were known to be alive at 5 years, those who died, those who were lost to follow-up, and those who withdrew.

final (10-year) analysis. A P value of less than 0.05 was considered to indicate statistical significance, without correction for multiple testing. 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 at 28 cardiac surgery centers in seven countries. A total of 1554 patients were randomly assigned to the single-graft group and 1548 to the bilateral-graft group. Figure 1 shows the flow of participants through the trial up to 5 years of follow-up. The groups were well matched with respect to age, sex, race and ethnic origin, body-mass index, systolic and diastolic blood pressure, smoking status, and coexisting conditions (Table 1).

TREATMENT

Data on surgical details and length of stay in the hospital[26] are provided in Table S1 in the Supplementary Appendix. In the single-graft group, 96.1% of the patients received a single internal-thoracic-artery graft, and in the bilateral-graft group, 83.6% of the patients received bilateral internal-thoracic-artery grafts. Off-pump procedures without the use of cardiopulmonary bypass were performed in 40.6% of patients. The rate of nonadherence to bilateral internal-thoracic-artery graft surgery was higher than expected. The mean number of grafts in each group was three. Medications at 5 years were well balanced between the two groups, with aspirin used in 88.9% of the patients, beta-blockers in 76.2%, statins in 89.0%, and angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers in 73.4% (Table S2 in the Supplementary Appendix).

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Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	Single-Graft Group (N=1554)	Bilateral-Graft Group (N=1548)
Age at randomization — yr	63.5±9.1	63.7±8.7
Male sex — no. (%)	1338 (86.1)	1318 (85.1)
Smoking status — no. (%)		
Current smoking	214 (13.8)	237 (15.3)
Former smoking	898 (57.8)	834 (53.9)
Never smoked	442 (28.4)	477 (30.8)
Race or ethnic group — no. (%)†		
White	1431 (92.1)	1418 (91.6)
East Asian	1 (0.1)	5 (0.3)
South Asian	76 (4.9)	74 (4.8)
Afro-Caribbean	2 (0.1)	0
African	1 (0.1)	4 (0.3)
Other	42 (2.7)	47 (3.0)
Missing data	1 (0.1)	0
Height — cm	170.4±8.4	170.0±8.5
Weight — kg	81.9±14.2	82.0±13.5
Body-mass index	28.1±4.1	28.3±4.0
Systolic blood pressure — mm Hg	131.8±18.5	131.7±18.0
Diastolic blood pressure — mm Hg	74.8±11.1	75.0±11.0
Diabetes — no. (%)		
No history	1191 (76.6)	1177 (76.0)
Insulin-dependent diabetes	79 (5.1)	95 (6.1)
Non–insulin-dependent diabetes	284 (18.3)	276 (17.8)
Hypertension treated with drugs — no. (%)	1217 (78.3)	1193 (77.1)
Hyperlipidemia treated with drugs — no./total no. (%)	1448/1554 (93.2)	1457/1547 (94.2)
Documented peripheral arterial disease — no. (%)	118 (7.6)	103 (6.7)
Documented transient ischemic attack — no./total no. (%)	57/1553 (3.7)	53/1548 (3.4)
Previous stroke — no./total no. (%)	48/1553 (3.1)	42/1548 (2.7)
Previous myocardial infarction — no./total no. (%)	681/1553 (43.9)	619/1547 (40.0)
Previous PCI, with or without stent — no./total no. (%)	248/1553 (16.0)	242/1547 (15.6)
NYHA functional class — no. (%)‡		
I	481 (31.0)	481 (31.1)
II	747 (48.1)	722 (46.6)
III	263 (16.9)	279 (18.0)
IV	61 (3.9)	66 (4.3)
Missing data	2 (0.1)	0
CCS angina class — no. (%)‡		
No angina	128 (8.2)	132 (8.5)
I	355 (22.8)	348 (22.5)
II	598 (38.5)	582 (37.6)
III	351 (22.6)	368 (23.8)
IV	122 (7.9)	118 (7.6)

* 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 two patients in the single-graft group and six in the bilateral-graft group; weight, for two in the bilateral-graft group; and blood pressure, for one in the single-graft group and three in the bilateral-graft group. PCI denotes percutaneous coronary intervention.
† Race or ethnic group was self-reported.
‡ New York Heart Association (NYHA) functional classes range from I to IV, with higher values indicating greater disability. Canadian Cardiovascular Society (CCS) angina classes range from I to IV, with higher values indicating more disabling pain due to angina.

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Table 2. Clinical Outcomes and Adverse Events at 5 Years.

Variable	Single-Graft Group (N=1554)	Bilateral-Graft Group (N=1548)	Hazard Ratio or Relative Risk (95% CI)*	P Value
	number (percent)			
Clinical outcome				
Primary outcome: death from any cause	130 (8.4)	134 (8.7)	1.04 (0.81–1.32)	0.77
Composite of death, myocardial infarction, and stroke	198 (12.7)	189 (12.2)	0.96 (0.79–1.17)	0.69
Myocardial infarction†	54 (3.5)	52 (3.4)	0.97 (0.66–1.41)	0.86
Stroke†	49 (3.2)	38 (2.5)	0.78 (0.51–1.19)	0.24
Adverse event				
Major bleeding	41 (2.6)	48 (3.1)	1.18 (0.78–1.77)	0.44
Repeat revascularization	103 (6.6)	101 (6.5)	0.98 (0.76–1.28)	0.91
Sternal wound complication	29 (1.9)	54 (3.5)	1.87 (1.20–2.92)	0.005
Sternal wound reconstruction	10 (0.6)	29 (1.9)	2.91 (1.42–5.95)	0.002

* Hazard ratios are presented for clinical outcomes, and relative risks for adverse events. Hazard ratios use the single-graft group as the control.

† These rows for clinical outcomes refer to all the events of myocardial infarction or stroke up to 5 years and not just those that form part of the composite. Since death is a competing risk for myocardial infarction or stroke, the analysis takes account of this, and therefore the hazard ratio refers to a subhazard ratio for these two rows.

OUTCOMES

A total of 5.1% of the trial participants (159 participants, including 84 in the bilateral-graft group and 75 in the single-graft group) had unknown vital status at 5 years because of loss to follow-up or withdrawal from the trial, although they do contribute to the analysis with a mean of 3.0 years of follow-up (Fig. 1). At 5 years of follow-up, there were 134 deaths (8.7%) in the bilateral-graft group and 130 deaths (8.4%) in the single-graft group (hazard ratio with the single-graft group as the control group throughout, 1.04; 95% confidence interval [CI], 0.81 to 1.32; P=0.77) (Table 2 and Fig. 2A). Results were similar after adjustment for age, sex, diabetes status, and ejection fraction (hazard ratio, 1.03; 95% CI, 0.81 to 1.32; P=0.80).

For the composite of death from any cause, myocardial infarction, or stroke, there were 189 (12.2%) in the bilateral-graft group and 198 events (12.7%) in the single-graft group (hazard ratio, 0.96; 95% CI, 0.79 to 1.17; P=0.69) (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. Approximately half the deaths were classified as being cardiovascular, with a hazard ratio that was similar to that in the analysis of all-cause mortality (Table S3 in the Supplementary Appendix).

An adjusted analysis of all-cause mortality on a per-protocol basis showed a hazard ratio of 1.01 (95% CI, 0.78 to 1.31) in the bilateral-graft group as compared with the single-graft group; in the as-treated analysis, the hazard ratio was 0.98 (95% CI, 0.76 to 1.26) (Table S4 in the Supplementary Appendix). Subgroup analyses did not show any evidence of significant interactions (Fig. 3).

The incidence of sternal wound reconstruction was 1.9% in the bilateral-graft group, as compared with 0.6% in the single-graft group (relative risk, 2.91; 95% CI, 1.42 to 5.95; P=0.002) (Table 2), and all these events occurred in the first year after surgery. Sternal wound complications occurred in approximately twice as many patients in the bilateral-graft group as in the single-graft group, whereas the rates of major bleeding events and the need for any repeat revascularization were similar in the two groups; the rate of repeat revascularization was just over 6% in each group (Table 2). Angina status at 5 years according to the WHO Rose angina questionnaire showed similar results in the two groups,

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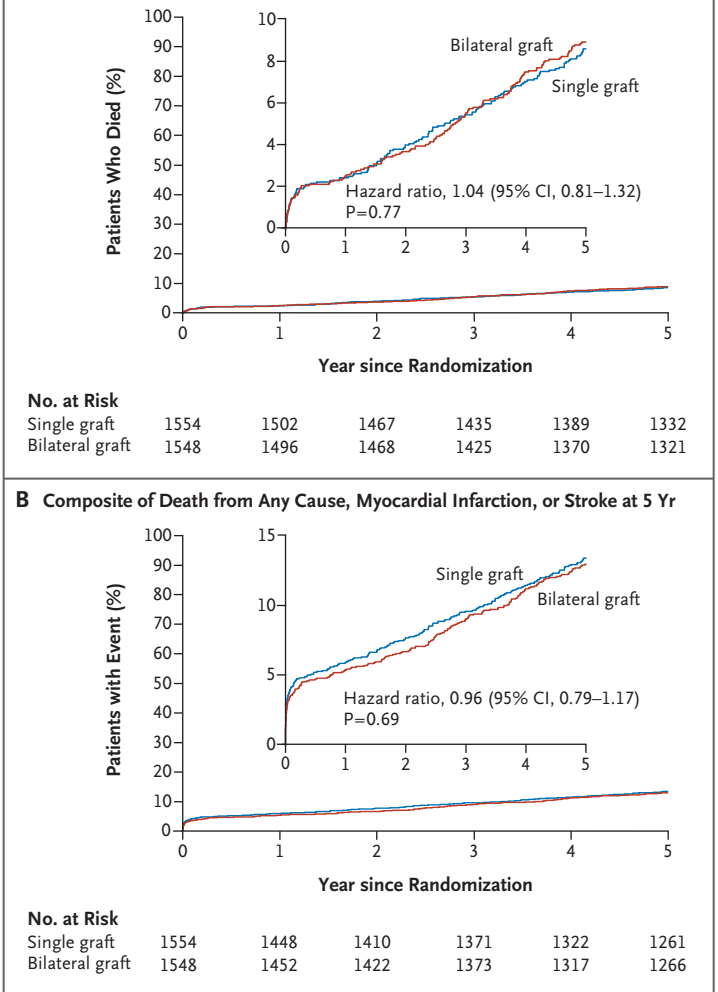

Figure 2. Primary Outcome of Death from Any Cause and Composite Outcome of Death from Any Cause, Myocardial Infarction, or Stroke.

Panel A shows the rate of death from any cause at 5 years, and Panel B the rate of the composite of death from any cause, myocardial infarction, or stroke at 5 years. Hazard ratios use the single-graft group as the control. Insets show the same data on an enlarged y axis.

with approximately 70% of the patients who responded to the questionnaire reporting no chest pain. Mean quality-of-life scores as assessed by the EQ-5D and SF-36 at 5 years showed no between-group differences for patients who provided data (Table S5 in the Supplementary Appendix).

DISCUSSION

In the ART, we randomly assigned patients undergoing CABG to single internal-thoracic-artery grafting or bilateral internal-thoracic-artery grafting. In this 5-year analysis, there were no significant differences between the two groups in all-cause mortality and in the composite rate of death from any cause, myocardial infarction, or stroke, even though bilateral internal-thoracic-artery grafting was associated with significantly higher rates of early sternal wound complications. Rates of major bleeding events and the need for repeat revascularization, angina status, and quality-of-life measures did not differ significantly between the two groups.

The surgical techniques that were used in this trial may influence the efficacy of CABG and subsequent outcomes. A post hoc analysis of the trial data at 1 year suggested that more careful dissection of the internal thoracic artery (the "skeletonized" technique) was associated with a lower risk of sternal wound complications regardless of whether single or bilateral internal-thoracic-artery grafts were used.[30] Also, a post hoc nonrandomized comparison from the trial showed similar rates of clinical events among patients receiving on-pump CABG and among those receiving off-pump CABG, with slightly higher rates of repeat revascularization among patients who underwent off-pump CABG.[31] Patients who underwent bilateral internal-thoracic-artery grafting tended to have lower rates of sternal wound complications if they underwent off-pump CABG than if they underwent on-pump CABG.[31] These observations are consistent with results of CORONARY (the CABG Off or On Pump Revascularization Study), in which 4572 patients were randomly assigned to undergo on-pump or off-pump CABG and which showed similar clinical outcomes at 1 year with numerically higher rates of repeat revascularization in the off-pump group.[32]

Long-term outcome after CABG, in spite of the widespread use of single internal-thoracic-artery grafting, is potentially limited by progressive reduction in the patency of vein grafts, which are commonly used for target vessels other than the left anterior descending coronary artery.[33] Bilateral internal-thoracic-artery grafting may provide better long-term outcomes than single internal-thoracic-artery grafting plus vein grafts because of the superior long-term patency of arterial grafts, as compared with vein grafts.[8,10] At 5 years, observational and randomized studies indicate that patency rates of both left and

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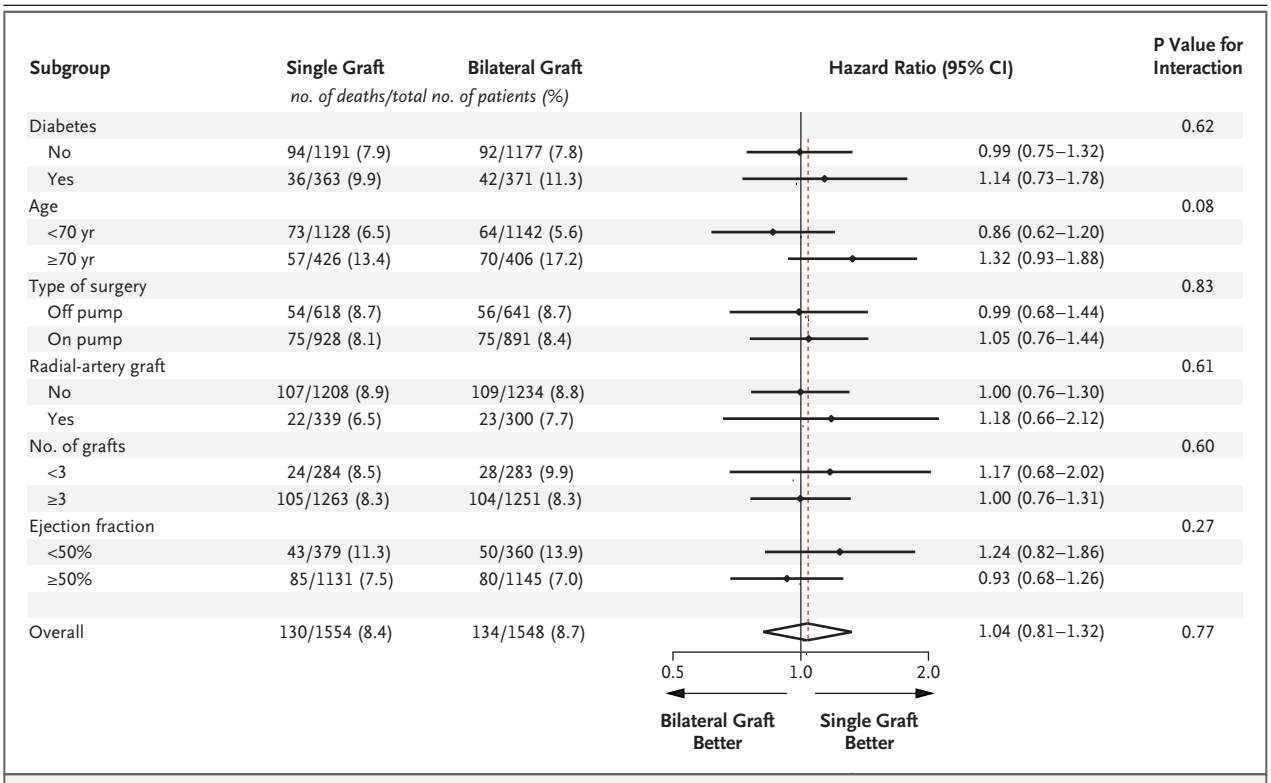

Figure 3. Subgroup Analysis of Death from Any Cause.

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 control. Data were missing as follows: type of surgery for 8 patients in the single-graft group and for 16 in the bilateral-graft group; use of radial-artery graft for 7 and 14, respectively; number of grafts for 7 and 14, respectively; and ejection fraction for 44 and 43, respectively. The overall P value is for the comparison of the two groups.

right internal-thoracic-artery grafts and of radial-artery grafts exceed 90%.[13,34-37] Vein-graft patency may also be improving over time, which may be related in part to better control of risk factors after CABG.[33] In the ART, the rates of use of aspirin, statins, beta-blockers, and ACE inhibitors (or angiotensin-receptor blockers) at 5 years were high. There are also concerns that the survival benefits of bilateral internal-thoracic-artery grafting, which may be apparent only over the long term, may be more difficult to show in older patients because of their shorter overall life expectancy.[38-40] Long-term follow-up is required in order to detect any clinical advantages from a second thoracic-artery graft.

Analysis of pooled observational data suggests that mortality is approximately 20% lower with bilateral grafts than with single internal-thoracic-artery grafts.[17-21] In spite of statistical corrections and propensity matching, these studies may be prone to bias in terms of patient and operator selection.[41] A post hoc analysis of the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial compared 5-year outcomes in 456 patients who received a second arterial conduit (74% of whom received bilateral internal-thoracic-artery grafting) with those in 963 patients who underwent single internal-thoracic-artery grafting with additional vein grafts.[42] After propensity-score adjustment, the incidence of major adverse clinical and cardiac events was 23.3% with bilateral grafts and 21.4% with single grafts (P=0.20), and the all-cause mortality was 9.1% and 9.5%, respectively (P=0.84). This subanalysis of the SYNTAX trial shows mortality results similar to those in the ART at 5 years, which suggests a similar risk profile of the patients who were enrolled in these trials.

The absence of any midterm benefit from bilateral over single internal-thoracic-artery grafting in our trial might have several explanations.

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First, the rate of vein-graft failure within 5 years may not be high enough to have an obvious adverse clinical effect. Second, there may not be a direct association between vein-graft failure and clinical events. Third, variation in surgeon experience may have reduced the effectiveness of bilateral grafting. In the ART, surgeons could adopt a variety of configurations for bilateral internal-thoracic-artery grafting that could influence efficacy. In practice, several configurations, including Y graft, free graft, and in situ configuration, are all associated with excellent patency rates.[43-45] Fourth, there may be little difference between the effects of the two techniques on clinical outcomes, owing to better long-term vein-graft patency, asymptomatic vein-graft failure, and improved medical therapy.

Several limitations of this trial should be considered. First, this planned interim analysis of an ongoing trial does not provide definitive long-term evidence regarding the comparison of CABG with the use of single versus bilateral internal-thoracic-artery grafting, which is still awaited. Second, at 5 years, the trial has less power to detect a difference in outcomes than is likely to be the case at 10 years, with consequent wide confidence intervals for the primary outcome. Third, more patients who were randomly assigned to bilateral grafting than to single grafting did not receive the assigned procedure (16.4% vs. 3.9%), and some expected loss to follow-up may reduce the power of the trial.[46]

In conclusion, in the ART, patients undergoing CABG were randomly assigned to receive either single internal-thoracic-artery grafting or bilateral internal-thoracic-artery grafting. At 5 years of follow-up, there were no significant differences in clinical outcomes between the two groups. There was some early excess of sternal wound complications in the bilateral-graft group. Ten-year follow-up is ongoing.

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

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REFERENCES

1. Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet 1994;344:563-70.
2. Taggart DP. Thomas B. Ferguson Lecture: coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. Ann Thorac Surg 2006;82:1966-75.
3. 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.
4. 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.
5. 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.
6. Cameron A, Davis KB, Green G, Schaff HV. Coronary bypass surgery with internal-thoracic-artery grafts — effects on survival over a 15-year period. N Engl J Med 1996;334:216-9.
7. Kurlansky P. Thirty-year experience with bilateral internal thoracic artery grafting: where have we been and where are we going? World J Surg 2010;34:646-51.
8. 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.
9. Weintraub WS, Jones EL, Craver JM, Guyton RA. Frequency of repeat coronary bypass or coronary angioplasty after CABG using saphenous vein grafts. Am J Cardiol 1994;73:103-12.
10. Gansera B, Schmidtler F, Angelis I, Kiask T, Kemkes BM, Botzenhardt F. Patency of internal thoracic artery compared to vein grafts — postoperative angiographic findings in 1189 symptomatic patients in 12 years. Thorac Cardiovasc Surg 2007;55:412-7.
11. Hlatky MA, Shilane D, Boothroyd DB, et al. The effect of internal thoracic artery grafts on long-term clinical outcomes after coronary bypass surgery. J Thorac Cardiovasc Surg 2011;142:829-35.
12. Kolesov VI, Kolesov EV. Twenty years' results with internal thoracic artery-coronary artery anastomosis. J Thorac Cardiovasc Surg 1991;101:360-1.
13. Glineur D, Papadatos S, Grau JB, et al. Complete myocardial revascularization using only bilateral internal thoracic arteries provides a low-risk and durable 10-year clinical outcome. Eur J Cardiothorac Surg 2016 April 15 (Epub ahead of print).
14. Lytle BW, Blackstone EH, Loop FD, et al. Two internal thoracic artery grafts are better than one. J Thorac Cardiovasc Surg 1999;117:855-72.
15. Lytle BW, Loop FD. Superiority of bilateral internal thoracic artery grafting: it's been a long time comin'. Circulation 2001;104:2152-4.
16. Buxton BF, Ruengsakulrach P, Fuller J, Rosalion A, Reid CM, Tatoulis J. The right internal thoracic artery graft — benefits of grafting the left coronary system and native vessels with a high grade stenosis. Eur J Cardiothorac Surg 2001;18:255-61.
17. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. Lancet 2001;358:870-5.
18. Takagi H, Goto SN, Watanabe T,

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Mizuno Y, Kawai N, Umemoto T. A meta-analysis of adjusted hazard ratios from 20 observational studies of bilateral versus single internal thoracic artery coronary artery bypass grafting. J Thorac Cardiovasc Surg 2014;148:1282-90.
19. Yi G, Shine B, Rehman SM, Altman DG, Taggart DP. Effect of bilateral internal mammary artery grafts on long-term survival: a meta-analysis approach. Circulation 2014;130:539-45.
20. Rizzoli G, Schiavon L, Bellini P. Does the use of bilateral internal mammary artery (IMA) grafts provide incremental benefit relative to the use of a single IMA graft? A meta-analysis approach. Eur J Cardiothorac Surg 2002;22:781-6.
21. Weiss AJ, Zhao S, Tian DH, Taggart DP, Yan TD. A meta-analysis comparing bilateral internal mammary artery with left internal mammary artery for coronary artery bypass grafting. Ann Cardiothorac Surg 2013;2:390-400.
22. Tabata M, Grab JD, Khalpey Z, et al. Prevalence and variability of internal mammary artery graft use in contemporary multivessel coronary artery bypass graft surgery: analysis of the Society of Thoracic Surgeons National Cardiac Database. Circulation 2009;120:935-40.
23. Vallely MP, Edelman JJB, Wilson MK. Bilateral internal mammary arteries: evidence and technical considerations. Ann Cardiothorac Surg 2013;2:570-7.
24. Tatoulis J, Buxton BF, Fuller JA. The right internal thoracic artery: is it underutilized? Curr Opin Cardiol 2011;26:528-35.
25. Taggart DP, Lees B, Gray A, Altman DG, Flather M, Channon K. Protocol for the Arterial Revascularisation Trial (ART): a randomised trial to compare survival following bilateral versus single internal mammary grafting in coronary revascularisation. Trials 2006;7:7.
26. Taggart DP, Altman DG, Gray AM, et al. Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). Eur Heart J 2010;31:2470-81.
27. Lawlor DA, Adamson J, Ebrahim S. Performance of the WHO Rose angina questionnaire in post-menopausal women: are all of the questions necessary? J Epidemiol Community Health 2003;57:538-41.
28. Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53-72.
29. Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's manual for the SF-36v2 Health Survey. 2nd ed. Lincoln, RI: QualityMetric, 2007
30. Benedetto U, Altman DG, Gerry S, et al. Pedicled and skeletonized single and bilateral internal thoracic artery grafts and the incidence of sternal wound complications: insights from the Arterial Revascularization Trial. J Thorac Cardiovasc Surg 2016;152:270-6.
31. Taggart DP, Altman DG, Gray AM, et al. Effects of on-pump and off-pump surgery in the Arterial Revascularization Trial. Eur J Cardiothorac Surg 2015;47:1059-65.
32. Lamy A, Devereaux PJ, Prabhakaran D, et al. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. N Engl J Med 2013;368:1179-88.
33. Domanski MJ, Borkowf CB, Campeau L, et al. Prognostic factors for atherosclerosis progression in saphenous vein grafts: the Postcoronary Artery Bypass Graft (Post-CABG) trial. J Am Coll Cardiol 2000;36:1877-83.
34. Tatoulis J, Buxton BF, Fuller JA. The right internal thoracic artery: the forgotten conduit — 5,766 patients and 991 angiograms. Ann Thorac Surg 2011;92:9-15.
35. 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.
36. Tatoulis J, Buxton BF, Fuller JA, et al. Long-term patency of 1108 radial arterial-coronary angiograms over 10 years. Ann Thorac Surg 2009;88:23-9.
37. 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.
38. Benedetto U, Amrani M, Raja SG. Guidance for the use of bilateral internal thoracic arteries according to survival benefit across age groups. J Thorac Cardiovasc Surg 2014;148:2706-11.
39. Mohammadi S, Dagenais F, Doyle D, et al. Age cut-off for the loss of benefit from bilateral internal thoracic artery grafting. Eur J Cardiothorac Surg 2008;33:977-82.
40. Kieser TM, Lewin AM, Graham MM, et al. Outcomes associated with bilateral internal thoracic artery grafting: the importance of age. Ann Thorac Surg 2011;92:1269-75.
41. Ioannidis JP, Galanos O, Katritsis D, et al. Early mortality and morbidity of bilateral versus single internal thoracic artery revascularization: propensity and risk modeling. J Am Coll Cardiol 2001;37:521-8.
42. Parasca CA, Head SJ, Mohr FW, et al. The impact of a second arterial graft on 5-year outcomes after coronary artery bypass grafting in the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery Trial and Registry. J Thorac Cardiovasc Surg 2015;150(3):597-606.e2.
43. Calafiore AM, Contini M, Vitolla G, et al. Bilateral internal thoracic artery grafting: long-term clinical and angiographic results of in situ versus Y grafts. J Thorac Cardiovasc Surg 2000;120:990-6.
44. Dion R, Glineur D, Derouck D, et al. Long-term clinical and angiographic follow-up of sequential internal thoracic artery grafting. Eur J Cardiothorac Surg 2000;17:407-14.
45. Sabik JF III, Stockins A, Nowicki ER, et al. Does location of the second internal thoracic artery graft influence outcome of coronary artery bypass grafting? Circulation 2008;118:Suppl:S210-S215.
46. Kappetein AP. Bilateral mammary artery vs. single mammary artery grafting: promising early results: but will the match finish with enough players? Eur Heart J 2010;31:2444-6.
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