

CORONARY BYPASS SURGERY WITH INTERNAL-THORACIC-ARTERY GRAFTS — EFFECTS ON SURVIVAL OVER A 15-YEAR PERIOD

AIRLIE CAMERON, M.D., KATHRYN B. DAVIS, PH.D., GEORGE GREEN, M.D., AND HARTZELL V. SCHAFF, M.D.

Abstract *Background.* Aortocoronary bypass surgery has been performed most often with the patient's saphenous vein as the conduit. The internal-thoracic-artery graft, which has superior patency rates, has been shown to have clinical advantages, but it is not known how long these advantages persist.

Methods. We identified all the patients in the registry of the Coronary Artery Surgery Study who had undergone first-time coronary-artery bypass grafting. Those with internal-thoracic-artery bypass grafts (749 patients) were compared with those with saphenous-vein bypass grafts only (4888 patients) with respect to survival over a 15-year follow-up period.

Results. In a multivariate analysis to account for differences between the two groups, the presence of an internal-thoracic-artery graft was an independent predictor of improved survival and was associated with a relative risk of dying of 0.73 (95 percent confidence in-

terval, 0.64 to 0.83). This improved survival was also observed in subgroups including patients 65 years of age or older, both men and women, and patients with impaired ventricular function. The survival curves of the two groups showed further separation over the years of follow-up, with a more marked downsloping after eight years in the curve for the group with saphenous-vein grafts only than in that for the group with internal-thoracic-artery grafts.

Conclusions. As compared with saphenous-vein coronary bypass grafts, internal-thoracic-artery grafts conferred a survival advantage throughout a 15-year follow-up period. The survival advantage increased with time, suggesting that the initial selection of the conduit was a more important factor in survival than problems appearing long after surgery, such as the progression of coronary disease. (N Engl J Med 1996;334:216-9.)

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THE internal thoracic artery (ITA) graft, which is used in coronary-artery bypass surgery, has been found in many single-institution clinical studies to be a superior conduit.¹⁻³ The Coronary Artery Surgery Study (CASS), a multicenter study with prospective clinical data in a large registry of 24,958 patients with suspected coronary artery disease, provides an opportunity to evaluate the ITA graft over a 15-year period in 15 centers. The extended follow-up makes it possible to determine whether the clinical benefit of the ITA graft persists or whether other factors, such as the progression of coronary disease in vessels not bypassed or in vessels distal to the graft anastomoses, have a more important bearing on survival.

METHODS

From the CASS registry, we identified the 8271 patients who had undergone first-time coronary-artery bypass grafting. Patients who had had repeated bypass surgery, those with congenital coronary anomalies, and those who had had associated cardiac surgery not involving the coronary arteries were excluded. Only patients with independent grafts with a single anastomotic site each were included. Excluded were 2131 patients with sequential grafts, 389 with Y-vein grafts, 16 with sequential ITA grafts, and 14 with double ITA grafts. A total of 2499 patients fell into one or more of these categories. We also excluded 17 patients whose survival times were unknown and 118 patients for whom inadequate details regarding grafts were available. The study groups to be compared thus included 4888 patients with one or more vein grafts, each with a single anastomotic site, and 749 patients with single ITA grafts, with or without associated vein grafts,

each with a single anastomotic site. All the vein grafts were reversed autogenous saphenous veins. There were no ITA implants or other arterial conduits. Beginning in 1974, follow-up information was obtained by mail and telephone interviews according to the CASS protocol.⁴ From 1988 to 1991, a questionnaire covering less detailed information was used.

Definitions used in the study have been reported elsewhere.⁵ Briefly, they are as follows. Operative mortality was defined as death within 30 days of surgery. Coronary-artery stenoses were considered clinically important if there was a visually estimated luminal narrowing of at least 50 percent of the diameter of the left main coronary artery or at least 70 percent in any other coronary-artery segment. Clinically important stenosis of the left main coronary artery was considered to constitute double-vessel disease. The left ventricular score was the sum of the scores for each of the five segments viewed in the 30-degree right anterior oblique projection, with each segment coded as follows: normal contractility, 1; moderate hypokinesis, 2; severe hypokinesis, 3; akinesis, 4; and dyskinesis, 5. Complete revascularization was considered to have been accomplished when all major vessels with clinically important stenosis were bypassed. Surgery was classified as elective, urgent, or emergency.

Statistical Analysis

Characteristics of the patient groups were compared by chi-square tests. Long-term survival was estimated by Kaplan-Meier methods. Variability in the estimates was indicated by point-wise confidence intervals at 15 years. Statistical comparisons of survival were made by the log-rank test. The Cox model was used to adjust for the effects on survival of other characteristics of the patients. The hazard function, which is the risk of dying within a short interval after a given time, was estimated nonparametrically with the use of life-table methods.⁶

RESULTS

Follow-up was 99 percent complete until 1982 and 94 percent complete when the questionnaire was used in the period 1988 to 1991. The duration of follow-up was up to 18.3 years (mean, 16.8). The clinical characteristics of the patients with ITA grafts and those without such grafts are shown in the univariate analysis in Table 1. Patients with ITA grafts were younger, had less impaired left ventricular function, less frequently had

From the Divisions of Cardiology and Cardiothoracic Surgery, St. Luke's-Roosevelt Hospital Center and the College of Physicians and Surgeons, Columbia University, New York (A.C., G.G.); the Departments of Biostatistics and Medicine, University of Washington, Seattle (K.B.D.); and the Mayo Clinic, Rochester, Minn. (H.V.S.). Address reprint requests to Dr. Cameron at the Division of Cardiology, St. Luke's-Roosevelt Hospital Center, 1111 Amsterdam Ave., New York, NY 10025.

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Table 1. Univariate Analysis of Characteristics of the Patients with ITA Grafts and Those with Vein Grafts Only.*

CHARACTERISTIC	PATIENTS WITH ITA GRAFTS (N = 749)	PATIENTS WITH VEIN GRAFTS (N = 4888)	P VALUE
	<i>percent</i>		
Age ≥ 65 yr	8	10	0.02
Stenosis of left main coronary artery $\geq 50\%$	10	14	0.001
Left ventricular score $>10^\dagger$	22	26	0.006
≥ 3 grafts	60	47	<0.001
Elective surgery	82	80	0.09
Proximal stenosis of left anterior descending artery	47	44	0.12
Triple-vessel disease	47	43	0.11
Female sex	16	17	0.49

*ITA denotes internal thoracic artery.

\dagger Left ventricular scores are explained in the Methods section.

clinically important stenosis in the left main coronary artery, and more often received three or more grafts. The proportions of patients with stenosis in the proximal left anterior descending artery, triple-vessel disease, and female sex were not significantly different in the two groups. We performed a multivariate analysis (Table 2) using a Cox proportional-hazards model with the covariates age, sex, left ventricular score, percent stenosis of the proximal left anterior descending artery, percent stenosis of the left main coronary artery, number of vessels that were diseased, number of grafts, surgical priority, and presence or absence of an ITA graft. The analysis identified the presence of an ITA graft as a significant predictor of survival ($P < 0.001$). The presence of an ITA graft reduced the risk of dying by a factor of 0.73 (95 percent confidence interval, 0.64 to 0.83).

Estimated rates of survival at 15 years (Table 3) were significantly higher for patients with ITA grafts, both for those with severely impaired ventricular function and for those with normal or near-normal ventricular function, both for men and for women, and both for younger and for older patients. A benefit was seen among patients without left main coronary-artery stenosis, but among those with left main coronary-artery stenosis of 50 percent or more, the estimated survival rates, although improved with ITA grafts, did not reach statistical significance.

Figure 1 shows the consistent separation of the cumulative survival curves for the patients with ITA grafts and for those without them; there is a further increase in the downslope of the curve for vein grafts only and thus more accelerated separation of the two curves beginning at eight years. To evaluate this trend, we estimated the hazard rates for each year

Table 2. Predictors of Mortality According to Cox Multivariate Analysis and Hazard Ratios.

PREDICTOR	P VALUE	HAZARD RATIO	95 PERCENT CONFIDENCE INTERVAL
Older age	<0.001	1.04	1.03–1.04
Higher left ventricular score	<0.001	1.08	1.07–1.09
More vessels diseased	<0.001	1.27	1.20–1.35
Absence of ITA graft	<0.001	1.37	1.20–1.56
Stenosis of left main coronary artery $\geq 50\%$	0.004	1.19	1.05–1.32
Female sex	0.011	1.15	1.03–1.28

after bypass surgery for the patients with vein grafts and for those with ITA grafts; these rates are shown in Figure 2. Both rates are high at the first time point in association with the operative mortality and fall to very low levels at the end of the first year. At each time point, the estimated hazard rate is lower for the patients with ITA grafts than for those with vein grafts. The difference appears to increase after eight years. The sudden change in the group with ITA grafts at years 13 and 15 is attributed to the small numbers of patients at risk at these time points.

DISCUSSION

This study, involving 15 clinical sites in United States and Canada, has shown that the use of the ITA as a bypass conduit in coronary surgery performed more than 15 years ago was an independent predictor of survival during the subsequent 15 years. The improved survival was seen among men as well as women, among younger as well as older patients, among those with well-preserved ventricular function and those with impaired ventricular function, and among those without clinically important disease of the left main coronary artery as well as in those with clinically important disease. Several of these subgroups are currently excluded at many centers from being considered to receive an ITA graft.

We have presented both survival estimates and hazard-rate estimates to show that the lower mortality rate for the patients with ITA grafts persisted after the initial

Table 3. Estimated Survival Rates at 15 Years.*

	PATIENTS WITH ITA GRAFTS			PATIENTS WITH VEIN GRAFTS		
	NO.	SURVIVAL (%)	95% CI	NO.	SURVIVAL (%)	95% CI
Left ventricular score †						
<10	575	71	67–71	3471	61	59–63
≥ 10	157	55	47–63	1236	43	40–45
Sex						
Male	626	68	64–71	4035	56	55–58
Female	123	63	54–71	853	55	51–58
Age						
≤ 65 yr	691	69	65–72	4379	59	57–60
> 65 yr	58	48	34–60	509	34	30–38
Stenosis of left main coronary artery						
$< 50\%$	674	69	65–72	4196	58	56–59
$\geq 50\%$	73	53	41–64	689	46	42–50

* $P < 0.05$ for all comparisons, with the exception of the comparison of patients with left main coronary-artery stenosis of at least 50 percent in the two groups, for which $P = 0.14$. ITA denotes internal thoracic artery, and CI confidence interval.

\dagger Left ventricular scores are explained in the Methods section.

perioperative period. After the first year, the hazard rates for both patient groups increased in an essentially linear fashion, but after the eighth year the hazard rate for the patients with vein grafts appeared to increase more rapidly than the rate for patients with ITA grafts. This is a time when there is a higher likelihood that saphenous-vein grafts will close,⁷⁻⁹ a factor that may account for the increasing difference. Vein grafts develop accelerated atherosclerosis and intimal fibrosis, whereas the ITA grafts have been shown at postmortem examination¹⁰ in all age groups to have little if any evidence of atherosclerosis.

This was an observational study, not a randomized trial. Thus, we cannot exclude the possibility that unmeasured variables may have contributed to the better outcome in the group with ITA grafts. However, when we used multivariate statistical techniques to account for important clinical differences between the two groups of patients, we still found a significant survival advantage associated with the use of an ITA graft.

These results showing improved survival with the ITA graft appear to demonstrate that the initial selection of an ITA graft has a more important influence on survival than factors that appear after surgery, such as the progression of coronary disease in vessels that were not bypassed or in bypassed vessels distal to the anastomoses. If the progression of coronary disease were the dominant force, then the curves would be expected to be similar.

The expanded use of the ITA with bilateral and sequential ITA grafts, with resultant multiple-vessel ITA anastomoses, may result in both further reduction in the frequency of clinical events and improvement in survival.¹¹ It seems reasonable to expect such a benefit because prolonged patency of the conduit is obviously required for improved survival. However, the added advantage of

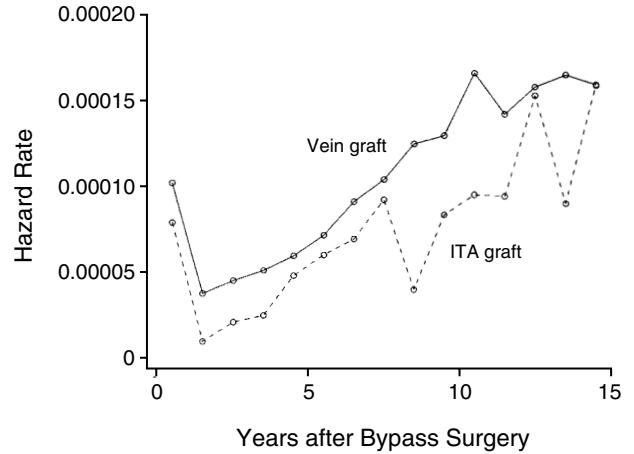


Figure 2. Estimated Hazard Rates for Each Year after Bypass Surgery for Patients with Internal-Thoracic-Artery (ITA) Grafts and Those with Vein Grafts.

a second or third ITA anastomosis is not expected to be as great as the enhanced benefit from the first anastomosis, since the first ITA graft will probably be selected to supply the left anterior descending coronary artery, which is the dominant vessel responsible for preserving ventricular function. Indeed, a 17-year follow-up study¹² of 1087 patients receiving bilateral ITA grafts showed an actuarial survival of 56.2 ± 5.9 percent, which is not much different from the result with a single ITA graft in this study. In the 17-year follow-up study, the patency rates for the right ITA grafts were lower than for the left ITA grafts (85 percent vs. 92 percent), perhaps affecting the follow-up results.

It will probably be necessary to follow large groups of patients for long periods to show a statistical difference in survival between patients receiving one ITA graft and those receiving two, and even longer to show a difference between patients with two ITA grafts and those with three or more. Of necessity, these grafts will have to be placed by surgeons expert in the techniques required for such small structures. There have been reports of decreased patency of right ITA grafts¹³ — undoubtedly a reflection of the surgical difficulties encountered in the use of this graft as opposed to the left ITA. Indeed, one study¹⁴ suggested that the operating microscope is a necessary tool in dealing with ITA–coronary anastomoses, and its use was an independent predictor of mortality over a 20-year follow-up period.

In spite of the passage of 15 years, the results of this study are applicable today. Although the current high

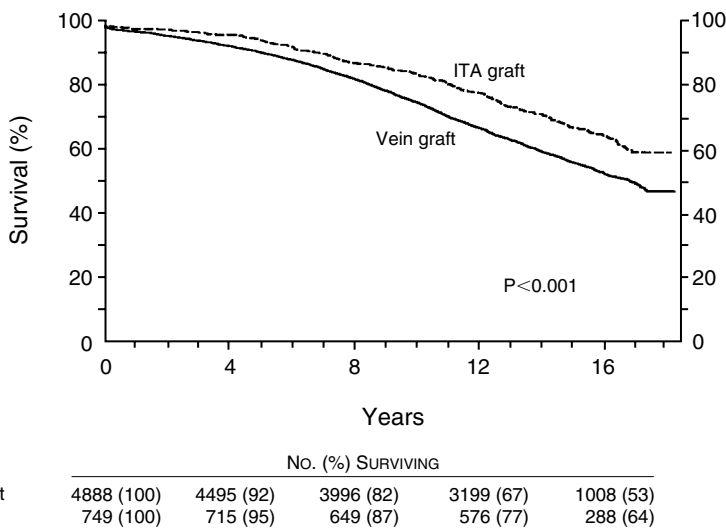


Figure 1. Estimated Survival Rates for Patients with Internal-Thoracic-Artery (ITA) Bypass Grafts and Those with Vein Grafts.

rate of percutaneous transluminal coronary angioplasty and other coronary interventions, as well as improved surgical techniques, has resulted in a shift in the pool of surgical candidates to include those with more adverse risk factors,¹⁵ these patients will benefit from the use of ITA grafts. In fact, in patients with a poor surgical outlook, it is most important to offer the benefit of an ITA graft. The ITA graft is a powerful surgical tool and should not be withheld from any subgroup of patients.

REFERENCES

1. Cameron A, Kemp HG JR, Green GE. Bypass surgery with the internal mammary artery graft: 15 year follow-up. *Circulation* 1986;74:Suppl III:III-30-III-36.
2. 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.
3. Zeff RH, Kongtahworn C, Iannone LA, et al. Internal mammary artery versus saphenous vein graft to the left anterior descending coronary artery: prospective randomized study with 10-year follow-up. *Ann Thorac Surg* 1988;45:533-6.
4. The Principal Investigators of CASS and their Associates. The National Heart, Lung, and Blood Institute Coronary Artery Surgery Study (CASS). *Circulation* 1981;63:Suppl I:I-1-I-39.
5. Cameron A, Davis KB, Green GE, Myers WO, Pettinger M. Clinical implications of internal mammary artery bypass grafts: the Coronary Artery Surgery Study experience. *Circulation* 1988;77:815-9.
6. Stata statistical software: release 4.0. College Station, Tex.: Stata Corporation, 1995:554.
7. Campeau L, Enjalbert M, Lesperance J, Vaislic C, Grondin CM, Bourassa MG. Atherosclerosis and late closure of aortocoronary saphenous vein grafts: sequential angiographic studies at 2 weeks, 1 year, 5 to 7 years, and 10 to 12 years after surgery. *Circulation* 1983;68:Suppl II:II-1-II-7.
8. FitzGibbon GM, Leach AJ, Kafka HP, Keon WJ. Coronary bypass graft fate: long-term angiographic study. *J Am Coll Cardiol* 1991;17:1075-80.
9. Lytle BW, Loop FD, Cosgrove DM, Ratliff NB, Easley K, Taylor PC. Long-term (5 to 12) years serial studies of internal mammary artery and saphenous vein coronary bypass grafts. *J Thorac Cardiovasc Surg* 1985;89:248-58.
10. Kay HR, Korn ME, Glemma RJ, Tector AF, Lepley D Jr. Atherosclerosis of the internal mammary artery. *Ann Thorac Surg* 1976;21:504-7.
11. Green GE, Cameron A, Goyal A, Wong S-C, Schwanede J. Five-year follow-up of microsurgical multiple internal thoracic artery grafts. *Ann Thorac Surg* 1994;58:74-9.
12. Galbut DL, Traad EA, Dorman MJ, et al. Seventeen-year experience with bilateral internal mammary artery grafts. *Ann Thorac Surg* 1990;49:195-201.
13. Huddleston CB, Stoney WS, Alford WC Jr, et al. Internal mammary artery grafts: technical factors influencing patency. *Ann Thorac Surg* 1986;42:543-9.
14. Cameron AAC, Green GE, Brogno DA, Thornton J. Internal thoracic artery grafts: 20-year clinical follow-up. *J Am Coll Cardiol* 1995;25:188-92.
15. Christakis GT, Ivanov J, Weisel RD, Birnbaum PL, David TE, Salerno TA. The changing pattern of coronary artery bypass surgery. *Circulation* 1989;80:Suppl I:I-151-I-161.