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SURGERY FOR ADULT CARDIOVASCULAR DISEASE

TWO INTERNAL THORACIC ARTERY GRAFTS ARE BETTER THAN ONE

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Objective: Does the use of bilateral internal thoracic artery (ITA) grafts provide incremental benefit relative to the use of a single ITA graft? **Methods:** We conducted a retrospective, nonrandomized, long-term (mean follow-up interval of 10 postoperative years) study of patients undergoing elective primary isolated coronary bypass surgery who received either single (8123 patients) or bilateral ITA grafts (2001 patients), with or without additional vein grafts. Multiple statistical methods including propensity score matching, and multivariable parsimonious and nonparsimonious risk factor analyses were used to address the issues of patient selection and heterogeneity. **Results:** In-hospital mortality was 0.7% for both the bilateral and single ITA groups. Survival for the bilateral ITA group was 94%, 84%, and 67%, and for the single ITA group 92%, 79%, and 64% at 5, 10, and 15 postoperative years, respectively ($P < .001$). Death, reoperation, and percutaneous transluminal coronary angioplasty were more frequent for patients undergoing single rather than bilateral ITA grafting, and this observation remained true despite multiple adjustments for patient selection, sampling, and length of follow-up. The differences between the bilateral and single ITA groups were greatest in regard to reoperation. The extent of benefit of bilateral ITA grafting varied according to patient-related variables, but no patient subsets were identified for whom single ITA grafting could be

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predicted to provide an advantage. Conclusions: Patients who received 2 ITA grafts had decreased risks of death, reoperation, and angioplasty. (J Thorac Cardiovasc Surg 1999;117:855-72)

The strategy of using the left internal thoracic artery (LITA) as a graft to the left anterior descending (LAD) coronary artery has become a standard part of coronary bypass surgery. LITA-LAD grafts have high long-term patency rates, graft atherosclerosis is rare, and clinical studies have demonstrated improved long-term survival and fewer repeat procedures and cardiac events for patients receiving LITA-LAD grafts.¹⁻⁴ Logic seems to dictate that adding the use of the right internal thoracic artery (RITA) as a bypass graft might further improve long-term outcomes. However, no studies have clearly demonstrated incremental benefits of bilateral ITA grafting over those achieved with an LITA-LAD graft combined with saphenous vein grafts.⁵⁻¹⁵

There are many possible reasons that it has been difficult to show a clinical advantage for the use of 2 ITA grafts, including (1) the success of the single ITA graft in achieving good outcomes for at least a decade, requiring relatively long-term follow-up in a large number of patients to demonstrate incremental benefit of multiple ITA grafts; (2) the multiple factors leading to the selection of patients to receive bilateral versus single ITA grafts confounds the interpretation of apparent benefits.

In this observational, nonrandomized study, we have compared outcomes for a large group of patients whose primary elective bypass surgery included either the use of 1 or both ITAs. The methods of comparison addressed pitfalls of using clinical experience to draw a casual inference that include (1) patient selection, potentially confounding the comparison, (2) patient heterogeneity influencing the overall estimate of any benefit because of patient mix, and (3) over-statement of the magnitude and certainty of any benefit contributed in part by the statistical methods used, as well as from the use of a single experience. The outcome end points that were studied were death from any cause, cardiac reoperation for any reason, and percutaneous treatment of coronary artery disease (percutaneous transluminal coronary angioplasty, or PTCA).

Patients and methods

Patient population. With the aid of a computerized prospective cardiovascular information registry, we identified all patients undergoing primary isolated revascularization using

both ITAs for bypass grafts during the years 1971 to 1989. Those patients are termed the bilateral ITA group. The first bilateral ITA operation at The Cleveland Clinic Foundation was performed in 1971. Entry to the study was stopped in 1989 to provide a minimum 6-year follow-up interval for all patients. Foreign patients were excluded from this group because of anticipated difficulty in follow-up. From the group of 2015 bilateral ITA patients identified, 14 patients were undergoing emergency operation and were excluded from further study because emergency operation is a factor that strongly affects the selection of patients for arterial graft operations. Therefore, aside from the exclusion of foreign patients and the 14 patients undergoing emergency operation, this represents a consecutive series of patients receiving bilateral ITA grafts as a primary operation for isolated bypass grafting.

In addition, through our cardiovascular information registry we have established a database of preoperative and perioperative data and have periodically conducted follow-up studies involving the first 1000 patients per year undergoing primary isolated elective (emergency operations excluded) coronary artery bypass grafting. From those 1000 patient cohorts undergoing surgery during the years 1971 to 1989, all patients were identified who received 1 ITA graft and at least 1 saphenous vein–coronary artery bypass graft. There were 8123 such patients, termed the single ITA group. Some foreign patients were included in these cohorts. Preoperative characteristics of both patient groups are listed in Appendix 1. No aspect of the surgical process was randomized for these patients. Multiple strategies for myocardial protection were used. The decision to use single or bilateral ITA grafts and the vessels that were chosen to be grafted with those ITAs were at the discretion of the attending surgeon.

In the bilateral ITA group, 1693 patients (84.6%) received 2 ITA grafts, 292 (14.6%) received 3, and 16 (0.8%) received 4. The ITAs were used entirely as in situ grafts for 1744 (87.2%) patients, 248 (12.4%) patients received 1 free ITA graft, and 9 received 2 free ITA grafts. Free grafts were performed as aorta–coronary grafts. Major target vessels for the ITA grafts were LAD and circumflex, 1217 patients (60.8%); LAD and right coronary artery (RCA), 459 patients (22.9%); and circumflex and RCA, 58 patients (3.0%). The rest of the patients (13.3%) received grafts that involved at least 1 ITA graft being used to graft a vessel classed as a diagonal coronary artery. Ramus, or intermediate arteries, fell into this classification. The details of the ITA grafting strategies are listed in Appendix 2. Nineteen patients (0.9%) who received concomitant gastroepiploic grafts and 4 (0.2%) who received radial artery grafts were excluded from the multivariable analyses at the request of one of the reviewers of this manu-

script. In the single ITA group the ITA was used as a graft to the LAD in 7147 patients, the LAD-diagonal in 144 patients, the circumflex in 220 patients, the diagonal branch in 588 patients, the RCA in 22 patients, and the diagonal-circumflex arteries in 2 patients. The patient numbers and percentages according to the number of saphenous vein grafts received were 0 saphenous grafts, 436 patients (21.8%); 1 graft, 750 patients (37.5%); 2 grafts, 599 patients (29.9%), 3 grafts, 182 patients (9.1%), 4 grafts, 31 patients (1.5%), and 5 saphenous grafts, 3 patients (0.1%).

Routine follow-up by mail with supplemental telephone follow-up has been conducted every 5 years for the single ITA group. Patients in the bilateral ITA group were followed up within 1 year of data analysis and had received at least 1 previous follow-up. Because of our interest in multiple arterial grafting, most patients in the bilateral ITA group had been followed up more than twice. The median follow-up interval of hospital survivors was 10.13 years (mean 9.71 ± 3.0 years) for the bilateral ITA group and 10.26 years (mean 10.80 ± 5.2 years) for the single ITA group. In the bilateral ITA group, follow-up was incomplete for 51 patients. Of these 51 patients, 6 had 1 to 5 years of postoperative follow-up, 34, 5 to 10 years, and 5 more than 10 years. In the single ITA group, 634 patients had incomplete follow-up, with 82 followed up for 1 to 5 years, 198 for 5 to 10 years, and 189 more than 10 years. The end points that were recorded were death from any cause, cardiac reoperation for any reason, and attempted percutaneous intervention for coronary artery disease (PTCA). When patients had incomplete follow-up they were censored at the date of last follow-up.

Logistic regression analysis was used to determine important predictors of in-hospital mortality. A logistic regression model, adjusted for age and ITA group, was then fit with only those variables that were significant in the stepwise model ($P < .05$) to allow the maximum number of patients to be analyzed. The odds ratios and 95% confidence intervals have been provided (Table I).

Analyses of time-related outcomes. The time-related outcome events used to compare single to bilateral ITA grafting were as follows: (1) death from any cause, including hospital deaths; (2) cardiac reoperations; (3) death or reoperation (reoperation-free survival); (4) percutaneous reinterventions (PTCA).

Nonparametric estimates of survival, freedom from cardiac reoperation, and freedom from PTCA were estimated for each group by the method of Kaplan and Meier.¹⁶ The instantaneous risk of events across time (the hazard function) was estimated by means of a parametric method that resolved the number of hazard phases, identified the shape of the hazard function, and estimated its parameters.¹⁷

Preliminary data analysis. Preliminary exploration of the data with respect to each event considered included frequency data of preoperative baseline characteristics using the χ^2 test to detect differences unlikely to be due to chance between the 2 ITA groups. Mean values of continuous variables, such as age, were compared by means of the Student t test.

Table I. Logistic regression analysis: In-hospital death

Variable	χ^2 P value	Odds ratio (95% CI)
BITA vs SITA	.5	0.81 (0.45, 1.46)
Age 50-60*	.5	1.33 (0.53, 3.37)
Age >60*	.01	2.98 (1.25, 7.10)
Gender (female)	<.001	2.51 (1.53, 4.14)
PVD	<.001	2.87 (1.71, 4.82)

CI, Confidence interval; BITA, bilateral internal thoracic artery group; SITA, single internal thoracic artery group; PVD, peripheral vascular disease.

*Compared with age less than 50 years.

Correlations were sought between variables. Life tables stratified by categorical variables were explored. Because naturally ordered variables, such as anginal symptoms and degree of left ventricular function, and all continuous variables were retained as such in the analyses, we investigated multiple transformations of these variables by decile risk analysis to best calibrate them in the risk factor models. These preliminary analyses were repeated in the case of hazard function analyses for events subdivided according to the time phase of their occurrence.

Data analysis. The primary objective of the data analysis was the statistical estimation of the possible benefit of bilateral ITA grafting on survival and freedom from interventions. Other objectives included the assessment of the effect of patient-related variables on outcome and the identification of definable patient subgroups with particularly great or particularly little benefit from bilateral ITA grafting. The analysis of possible benefit addressed *confounding* (patient selection) by use of a propensity score,¹⁸ *heterogeneity* (risk factors) by multivariable risk factor analysis,¹⁹ and *shrinkage* (exaggeration of benefit) by bootstrap resampling.²⁰

Confounding (patient selection). Because use of bilateral versus single ITA grafting did not involve randomized assignment, patient selection bias was addressed by a matching strategy for which a propensity score was used.¹⁸ The event bilateral ITA (vs single ITA) grafting was analyzed, without regard to any outcome, using logistic multivariable regression. The object was not to develop a parsimonious risk factor model, but to account for all known sources of potential selection bias. Nevertheless, to accomplish this, a sequence of intermediate modeling efforts was needed. First, a parsimonious model of individual factors ("main effects") was developed independently by P.H. and E.B. and the models were reconciled. All factors listed in Appendix 3 were used, but unlike the subsequent multivariable analyses of outcomes, variables for individual surgeons were also incorporated, because they could be considered a source of selection bias. Second, interactions among the variables in the parsimonious model were sought, these being dominated by age of the patient and date of the operation. Finally, risk factors not represented in the parsimonious model were incorporated. These additional variables included anginal symptoms, history of myocardial infarction, family history of coronary artery disease, left main disease, hypertension, and chronic obstruc-

Fig 1. Comparison of the bilateral ITA (BITA) and single ITA (SITA) groups in terms of survival (A) and reoperation-free survival (B). Numbers of patients surviving at selected follow-up intervals are listed beneath part A.

tive pulmonary disease. The area under the receiver operating characteristic (ROC) curve for this model was 0.91.

After completion of the propensity model, a propensity score was calculated from the logistic equation for each patient. The model predicted likelihoods of bilateral ITA grafting (vs single ITA grafting) ranging from essentially 0% to 99.7%. As suggested by Rubin,²¹ the patients were sorted by propensity and compared within quintiles. Only 68 patients receiving bilateral ITA grafting were in the first 2 quintiles. However, bilateral and single ITA patients in quintiles 3 through 5 were well matched with respect to patient risk factors. Appendix 4 details the matching of quintiles 3 through 5 in regard to *selected* variables, but the bilateral ITA–single ITA groups were similarly well matched for all variables in Appendix 3. Thus the sample of “propensity-matched patients” excludes the first 2 quintiles of single ITA patients (3976 patients). The excluded patients were predicted to receive bilateral ITA grafting with low probability for any of a variety of reasons, and essentially did not match bilateral ITA grafting cases for comparison purposes. The propensity score was either retained as a logit unit score or

transformed into the probability domain (as the probability of receiving bilateral ITA grafting). It was incorporated as a continuous variable into outcomes analyses described below to adjust for possible confounding.²²

Heterogeneity (risk factors). A number of risk factors (case mix) influence each of the outcomes studied; the prevalence of some of these differed between the groups (Appendix 1). These differences may have increased or reduced the apparent benefit of bilateral versus single ITA grafting. Importantly, these factors also could give insight into the nature of the treatment and predict which patients are more or less likely to benefit from treatment. Therefore risk factor models were developed for the separate events, death, reoperation, and PTCA.

Two multivariable risk factor models were used for 2 different purposes. Semiparametric Cox proportional hazards regression was used to obtain *average* effects across time.²³ Interactions of variables with the type of ITA grafting were not considered to obtain a simple estimate of a possible benefit of bilateral ITA grafting in the form of a single parameter estimate. The second method used parametric, multiphase, nonproportional hazards regression to obtain time-specific effects.¹⁷

For the Cox proportional hazards regression, initial screening of potential risk factors was accomplished by forward stepwise regression, followed by examination of interaction terms. For the nonproportional hazards regression, a directed technique of entry of variables into the multivariable risk factor model was used.¹⁸ Both forward stepwise and backward variable elimination analysis supplemented this directed technique, identifying the same model. Interactions among variables were sought thereafter, including interactions with type of grafting.

For the Cox proportional hazards model, results are presented in terms of the regression coefficients ± 1 standard error and the hazard ratio and 95% confidence limits. Nonproportional hazard regression coefficients are presented ± 1 standard error in a phase-specific fashion. The *P* value criterion for retention of variables and interactions in the final models was .05 for either method.

While these modeling efforts were performed quasi-independently, after the development of each, differences between models were examined, and the differences were either reconciled or understood as genuine differences in the models. Thus all final models represent the end product of a joint statistical collaborative effort.

Confounding and heterogeneity. To maximally adjust the estimate of possible benefit of bilateral ITA grafting, *nonparsimonious* regression models were developed in both the Cox proportional and the parametric nonproportional hazards domains with both the type of ITA grafting forced into the model, as well as the most appropriate transformation of the propensity score. Initially parsimonious models were developed using a *P* value criterion of .1, followed by investigation of interaction terms (including interactions with type of grafting in the case of the parametric nonproportional hazards

Table II. Incremental risk factors for death (Cox proportional hazards model for all patients), $N = 10,098$ (8123 SITA, 1975 BITA)

Incremental risk factors	Coefficient $\pm$ SD	Hazard ratio	95% CL	P value
Demography				
Women	0.162 $\pm$ 0.32	5.05	2.67-9.53	<.0001
Age				
Older	0.100 $\pm$ 0.01	1.11	1.09-1.12*	<.0001
Younger	1.01 $\pm$ 0.13	2.76	2.12-3.58†	<.0001
Women + younger age (interaction)	-0.024 $\pm$ 0.005	0.98	0.97-0.99‡	<.0001
Greater body mass index	0.006 $\pm$ 0.002	1.01	1.00-1.01	.004
Symptoms of reversible ischemia				
More severe angina class	0.04 $\pm$ 0.02	1.05	1.01-1.08§	.01
Coronary disease				
Greater left main disease	0.42 $\pm$ 0.08	1.52	1.30-1.77	<.0001
Right coronary artery occlusion $\geq$ 50%	0.113 $\pm$ 0.06	1.12	1.00-1.25	.048
Circumflex occlusion $\geq$ 70%	0.23 $\pm$ 0.04	1.26	1.16-1.37	<.0001
Left ventricular function				
Higher grade of dysfunction	0.41 $\pm$ 0.10	1.51	1.23-1.85¶	<.0001
+ Younger age (interaction)	-0.20 $\pm$ 0.08	0.82	0.69-0.97#	.02
Chronic heart failure	0.60 $\pm$ 0.08	1.81	1.55-2.12	<.0001
History of myocardial infarction	0.182 $\pm$ 0.04	1.20	1.10-1.31	<.0001
Noncardiac comorbidity				
Peripheral vascular disease	0.44 $\pm$ 0.05	1.56	1.40-1.73	<.0001
Smoking history	0.41 $\pm$ 0.04	1.50	1.38-1.63	<.0001
Pharmacologically treated diabetes	0.29 $\pm$ 0.12	1.33	1.06-1.68	.02
+ Younger age (interaction)	0.47 $\pm$ 0.14	1.59	1.20-2.11**	.001
Hypertension	0.34 $\pm$ 0.05	1.41	1.27-1.56	<.0001
Operation				
Single ITA grafting	0.186 $\pm$ 0.06	1.20	1.07-1.35	.001
ITA to LAD	-0.122 $\pm$ 0.06	0.88	0.79-0.99	.04
Experience				
Earlier date of operation	0.087 $\pm$ 0.03	1.09	1.03-1.15††	.002

CL, Confidence limits; ITA, internal thoracic artery.

*Per 1-year increase.

†Per unit change in $[50/\text{age}]^2$ inverse squared transformation.

‡Per 1-year decrease (interaction in female patients).

§Per unit increase in anginal severity.

||Per change from 0% to 100% [percent stenosis/100] scaled transformation.

¶Per unit increase in dysfunction.

#Per unit decrease in $[\text{age}/50]^2$ scaled transformation (interaction with dysfunction).

**Per unit change in $[50/\text{age}]^2$ inverse squared transformation (decrement in diabetic patients).

††Per unit change in $[1/\text{years since 1971}]$ inverse transformation.

modeling). Interactions were included only for $P < .05$. In general, the variables found in the parsimonious aspects of this modeling effort were identical to those in the analysis of heterogeneity. Subsequently, variables were added to the model, irrespective of P value, from each category of variables. Thus the final models always included gender, age (or its transformation), body size (height or weight, whichever was more significant), grade of anginal symptoms, degree of left ventricular dysfunction, presence of congestive heart failure, history of previous myocardial infarction, family history of coronary disease, smoking history, peripheral vascular disease, diabetes, hypertension, one or more variables concerning the extent of coronary artery disease, date of operation, and location of ITA grafts. In the case of the parametric non-proportional hazards model, the same procedure was fol-

lowed for the hazard phase containing the largest number of events; however, in the case of phases containing few events, only that number of additional variables was added that was less than half the number of events identified for that phase.

Shrinkage (exaggeration of benefit). All these analyses were performed on the same groups of patients. This has the disadvantage that the apparent benefit may be inflated and the variance estimate too small, resulting in P values for the difference that are smaller than might be found in repeated similar experiences. Various methods have been developed, therefore, to “shrink” the estimates, yielding a more conservative, but probably more accurate, estimate of benefit. In this study, multiple patient samples, each equal in number to the total propensity-matched sample size, were randomly drawn from the existing patient population. Each sample was then ana-

Fig 2. Comparison of survival and reoperation hazard function curves in the propensity-matched patients (both $P < .0001$) (bilateral [BITA], $n = 1989$; single [SITA], $n = 4147$). CABG, Coronary artery bypass grafting.

Table III. Average comparative risk of single vs. bilateral ITA grafting based on Cox proportional hazards methodology

Method of adjustment	Death		Reoperation		PTCA	
	HR	95% CL	HR	95% CL	HR	95% CL
1. None, entire population, all follow-up	1.36	1.21-1.52	3.87	2.87-5.21	1.02	0.83-1.25
2. None, entire population, 12-year follow-up	1.42	1.27-1.60	3.83	2.81-5.22	0.95	0.78-1.17
3. None, propensity-matched group	1.67	1.47-1.89	3.63	2.63-5.00	1.27	1.02-1.59
4. For confounding only	1.30	1.12-1.51	3.68	2.66-5.10	1.43	1.14-1.79
5. For heterogeneity only (parsimonious)	1.33	1.17-1.51	4.39	2.96-6.52	1.79	1.42-2.26
6. For confounding and heterogeneity (nonparsimonious)	1.36	1.17-1.57	4.67	3.14-6.96	1.79	1.43-2.26
7. For confounding and heterogeneity, bootstrap (nonparsimonious)	1.35	1.16-1.56	4.91	3.30-7.55	1.84	1.46-2.30

CL, Confidence limits; HR, hazard ratio; ITA, single internal thoracic artery graft.

lyzed as though it were a new patient population and all coefficients of the proportional and nonproportional hazards models adjusted for confounding and heterogeneity. This sampling and analysis process was repeated 1000 times. This computer-intensive process called *bootstrapping* yielded the most conservative estimate of the effect of arterial grafting strategy.²⁰

Data in figures are presented with confidence limits equivalent to 1 standard error. In tabular data means are presented ± 1 standard deviation.

Results

Patient characteristics. Appendix 1 shows the univariate comparisons of the baseline differences between the entire bilateral ITA and single ITA groups. There were statistically significant differences in regard to gender, age, incidence of diabetes, family history of coronary artery disease, preoperative functional class, left ventricular function status, extent of disease (num-

ber of vessels stenotic), and greater than 70% LAD lesion (all $P < .001$). All variable subgroups were well represented in both the bilateral and single ITA groups except that there were a small number of patients in the bilateral ITA group who were 70 years old or older (62 patients).

In-hospital morbidity and mortality. Hospital death occurred in 14 patients (0.7%) in the bilateral ITA group and 58 patients (0.7%) in the single ITA group. Table I contains the results of logistic regression analysis of the variables in Appendix 1 in regard to their influence on in-hospital mortality. The number of ITAs used as grafts was not associated with mortality. The only morbid event significantly different between the 2 groups was sternal wound complications (bilateral ITA 50/2001, 2.5%, vs single ITA 115/8123, 1.4%) ($P = .001$).

Survival and reoperation. Late survival for the entire bilateral ITA and single ITA groups is shown in

Fig 3. Distribution of Cox hazard ratios for 1000 “bootstrap” samples tested for the influence of bilateral versus single ITA grafts on the occurrence of death, PTCA, and reoperation. Any Cox hazard ratio greater than 1 indicates an advantage for bilateral ITA grafting. All hazard ratios for all samples were greater than 1.

Fig 1, along with the number of patients surviving at selected follow-up intervals. Patients receiving a single ITA graft had a higher late mortality than the patients receiving bilateral ITA grafts. Risk factors for survival were examined with a Cox regression (parsimonious) multivariate model that included all patients (none removed by virtue of propensity score) shown in Table II. Parametric, nonproportional hazard models involving all patients produced similar results.

The survival curves for the *propensity-matched* bilateral ITA and single ITA groups are shown in Fig 2.

Forty-six of the patients in the bilateral ITA group underwent cardiac reoperation. For 32 patients the reoperation was carried out solely for bypass grafting, and the anatomic indications for surgery were progression of native vessel disease without graft failure ($n = 2$), graft failure alone ($n = 9$), a combination of native vessel disease progression ($n = 17$), and unknown reasons ($n = 4$). Of the 14 remaining patients who underwent reoperation, the repeat procedure was for a valve or aortic aneurysm surgery alone in 7. The other 7 patients underwent valve surgery and also received bypass grafting, but in 4 of the patients the bypass grafting was incidental. Reoperation-free survival of the entire bilateral ITA and single ITA groups is shown in Fig 1. Hazard-function curves for reoperation for the propensity-matched groups are shown in Fig 2.

Analyses of differences in outcomes. The simplest question of the study (Are 2 ITA grafts better than 1?) is addressed quantitatively in Table III by means of multiple statistical approaches. This table presents the hazard ratios from Cox proportional hazard regression models for each outcome (death, reoperation, PTCA)

and includes (1) a nonadjusted estimate based on the entire bilateral ITA and single ITA population for all follow-up available, (2) a nonadjusted estimate for the entire population with follow-up truncated to 12 years (because of small numbers of bilateral ITA patients followed up for more than 12 years), (3) a nonadjusted estimate for the propensity-matched patients for 12 years, (4) estimates adjusted for confounding only in the propensity-matched groups (using the propensity score), (5) estimates based on traditional parsimonious modeling of the propensity-matched groups, (6) estimates based on nonparsimonious adjustments for both confounding and heterogeneity, and, finally, (7) estimates based on the 1000 nonparsimonious bootstrap models drawn from the propensity-matched groups adjusted for both confounding and heterogeneity. The benefit of bilateral ITA grafting is expressed by the hazard ratio whose value is equal to 1 if the average outcomes are equivalent and greater than 1 if outcomes are better with 2 ITA grafts. The last line in Table III produces the most conservative and believable set of estimates. However, regardless of the adjustment techniques used, the estimates are fairly similar and in all cases outcomes were better for the patients with 2 ITA grafts.

Bootstrap resampling was used to create 1000 different patient populations to see if any of the populations would exhibit a Cox regression hazard ratio of less than 1, indicating superiority of a single ITA graft for that population. None did. The distribution of the Cox hazard ratios for these bootstrap samples is shown in Fig 3.

The preceding analyses were designed to answer the single question of the relative advantage of having 2

Table IV. Incremental risk factors for death (nonproportional hazards parsimonious model): Propensity-matched patients

Incremental risk factor	Hazard phase			
	Early	P	Late	P
Demography				
Women	↑	.0004	—	—
Age				
Older	↑	<.0001	↑	<.0001
Younger	—	—	↑	.01
Symptoms of reversible ischemia				
More severe angina class	—	—	↑	.003
Coronary disease				
Greater left main disease	—	—	↑	.02
Larger number of diseased systems	—	—	↑	.006
Left ventricular function				
Higher grade of dysfunction + Younger age (interaction)	↑	<.0001	↑	<.0001
Chronic heart failure	—	—	↑	.004
History of myocardial infarction	—	—	↑	<.0001
History of myocardial infarction	—	—	↑	.01
Noncardiac comorbidity				
Peripheral vascular disease	↑	<.0001	↑	<.0001
Smoking history	—	—	↑	<.0001
Pharmacologically treated diabetes	—	—	↑	.02
+ Older age (interaction)	—	—	↑	.02
+ Younger age (interaction)	—	—	↑	.002
Hypertension	—	—	↑	<.0001
Operation				
Single ITA grafting	—	—	↑	<.0001
ITA to LAD	↓	.01	—	—
Experience				
Earlier date of operation	↑	.03	—	—

ITA, Internal thoracic artery; LAD, left anterior descending coronary artery.

ITA grafts. To put that strategy in the context of other risk factors, we studied the propensity-matched patient sample with detailed risk factor analyses (parsimonious multivariate models). Both Cox regression and nonproportional hazard models confirmed that a single ITA graft was a risk factor for all outcomes, but the level of risk of a single ITA graft was estimated to be higher by the nonproportional hazards method because that method isolates its influence more specifically to the late rising hazard phase. Nonproportional hazard models for the propensity-matched groups were developed in regard to death (Table V), reoperation (Table VI), and PTCA (Table VII).

Magnitude of the benefit of bilateral ITA grafting. Because the occurrence of death, reoperation, and PTCA are related to multiple variables other than surgical strategy, estimation of the extent of benefit from

Table V. Incremental risk factors for reoperation (nonproportional hazards parsimonious model): Propensity-matched patients

Incremental risk factor	Hazard phase			
	Early	P	Late	P
Demography				
Younger age	—	—	↑	.003
Shorter height	—	—	↑	.01
Left ventricular function				
Chronic heart failure	—	—	↑	.01
Noncardiac comorbidity				
Hypertension	↑	.02	—	—
Operation				
Single ITA grafting	↑	.003	↑	<.0001
ITA to LAD	—	—	↓	.004
ITA to RCA	—	—	↑	.01
Experience				
Earlier date of operation	↑	.07	—	—

ITA, Internal thoracic artery; LAD, left anterior descending coronary artery; RCA, right coronary artery system.

Table VI. Incremental risk factors for percutaneous procedure (PTCA) (nonproportional hazards parsimonious model)

Incremental risk factor	Late hazard phase	P
Demography		
Younger age	↑	<.0001
Coronary disease		
RCA stenosis	↓	.002
Left ventricular function		
Lower grade of dysfunction	↑	.0004
History of myocardial infarction	↓	.01
+ Older age (interaction)	↑	.01
Operation		
Single ITA grafting	↑	<.0001
Experience		
More recent date of operation	↑	<.0001

PTCA, Percutaneous transluminal coronary angioplasty; RCA, right coronary artery system; ITA, internal thoracic artery.

bilateral ITA grafting must adjust for these variables. Nonproportional hazard equations were developed for each patient in the propensity-matched population. All the information regarding the variables in Appendix 3 were included in the equation, and that equation was then solved twice—once as if the patient had received 1 ITA graft and once as if he or she had received 2 ITA grafts. The predicted percentage difference in the occurrence of death, reoperation, and PTCA by 12 postoperative years on the basis of 1 versus 2 ITA grafts was then calculated for each patient. Those percentage differences are depicted in Fig 4, plotted against the proportion of the population predicted to

Fig 4. Nonproportional hazard equations were solved twice for each propensity-matched patient, once as if the patient had single ITA grafting and once as if the patient had bilateral ITA grafting. The distribution of the percentage differences in outcomes for all patients based on bilateral versus single ITA grafting are shown in this figure. All patients had better predicted outcomes with bilateral ITA grafting. The percentage of the patient population is expressed vertically and the percent difference in the occurrence of each event is expressed horizontally. The table details percent differences at selected percentages of the entire patient population.

Fig 5. Non-risk-adjusted age relation to survival and freedom from reoperation at 12 postoperative years for propensity-matched patients based on nonproportional hazard equations. The survival curve confidence limits of patients having bilateral (BITA) and single (SITA) ITA grafting overlap at young ages. Bilateral ITA grafting produces significantly better freedom from reoperation at all ages and better survival at older ages.

experience that percentage difference in each event. Bilateral ITA grafting was most protective against reoperation. However, for all patients bilateral ITA grafting was predicted to produce better outcomes in regard to all adverse events (death, reoperation, PTCA).

Examination of bilateral ITA grafting for specific subgroups. Fig 4 indicates that although all patients are estimated to have better outcomes with bilateral ITA grafting, for some that benefit is relatively small, particularly in regard to survival. Important prognostic variables were examined to try to identify “low bene-

Fig 6. Non-risk-adjusted survival curves for diabetic and nondiabetic patients according to bilateral (*BITA*) versus single (*SITA*) ITA grafting at 12 postoperative years. For both groups survival for patients having bilateral ITA grafting was better.

Fig 7. Twelve-year survival of patients having bilateral (*BITA*) or single (*SITA*) ITA grafting according to left ventricular (*LV*) function (none or mild dysfunction vs moderate or severe dysfunction). For both ventricular function subgroups, survival was better for patients having bilateral ITA grafting.

fit" groups. Fig 5 illustrates the non-risk-adjusted relationship of age to survival and freedom from reoperation by 12 postoperative years for the propensity-matched patients. For younger patients the improvement in survival was small, as both bilateral ITA and single ITA groups had favorable survival; however, younger patients in the single ITA group were at a very high risk for reoperation, and bilateral ITA grafting greatly decreased that risk. As patients aged the risk of reoperation became less and the risk of death became greater along with an increase of the effect of bilateral ITA grafting in improving survival.

We also examined the propensity-matched patients in regard to diabetes and left ventricular function. Fig 6 depicts survival for the bilateral ITA and single ITA groups in regard to survival, showing that bilateral ITA grafting produces improved outcomes for patients with or without pharmacologically treated diabetes. Fig 7 examines unadjusted survival stratified by left ventricular dysfunction (none or mild vs moderate or severe). Again, the bilateral ITA grafting improves survival for both subsets.

Thus, although the analyses depicted in Figs 3 and 4 indicate that "low benefit" groups do exist, particularly

Fig 8. Predicted survival and reoperation hazard function curves according to 1 ITA versus 2 ITAs for a 47-year-old normotensive man with 2-vessel disease and normal left ventricular function (patient 1) and for a 64-year-old hypertensive man with 3-vessel disease and moderate impairment of left ventricular function (patient 2). CABG, Coronary artery bypass grafting.

Fig 9. Predicted survival and reoperation hazard function curves, 1 ITA versus 2 ITAs, for a normotensive 70-year-old man with normal left ventricular function (patient 3) and a 50-year-old hypertensive man with severe left ventricular dysfunction and a history of congestive heart failure (patient 4).

in regard to survival, those groups are not completely defined by the use of a single variable. Multiple variables are required to predict high and low benefit groups.

For illustration we used nonproportional hazard equations (Tables IV and V) to examine the difference based on bilateral versus single ITA grafting for patients defined by multiple characteristics. Fig 8 depicts predicted outcomes for patient 1 (a 47-year-old normotensive man with normal left ventricular function, class II angina, and 2-vessel disease) and patient 2

(a 64-year-old hypertensive man with a previous myocardial infarction, 3-vessel disease, and moderate impairment of left ventricular function). Patient 1 is predicted to have excellent survival regardless of whether he receives 1 or 2 ITA grafts, but he has a much higher likelihood of reoperation (approximately 10% $\times$ 12 postoperative years) if he receives a single ITA graft. Patient 2 has a worse survival outlook overall, but the risks of death and reoperation are both significantly decreased by the use of 2 ITA grafts. Age,

however, is not the only important predictor. Fig 9 depicts outcomes for 2 patients with 3-vessel disease and class III angina. Patient 3 is a 70-year-old man with normal left ventricular function and patient 4 is 50 years old with severe left ventricular dysfunction, a history of hypertension, and heart failure. Both patients are predicted to have improved survival with bilateral ITA grafting (patient 4 more than patient 3), and although both patients are also at a decreased risk of reoperation with bilateral ITA grafting, again, patient 4 benefits more than patient 3.

Discussion

Few randomized prospective studies have been conducted concerning any of the variations in the basic strategies of coronary bypass surgery. However, a myriad of observational data has confirmed the effectiveness of the LITA-LAD graft in terms of superior long-term patency and its importance clinically in decreasing the risks of late death and cardiac events after bypass surgery, even when used in conjunction with saphenous vein grafts to the circumflex and RCA systems.¹⁻⁴ On the basis of logic, many surgeons have used simultaneous bilateral ITA grafts for selected patients. However, although the use of that strategy dates back to the early years of bypass surgery, the idea that it will improve long-term outcomes has not been supported by convincing clinical data, despite the efforts of a number of experienced investigators.^{5-8,12-15,24-26}

A major issue in the investigation of the relative benefits of single versus bilateral ITA grafting is patient selection. Even advocates of bilateral ITA grafting have not used this strategy for all patients, and the possibility that differences in long-term outcomes are based on patient-related variables or the period of the operation rather than operative strategy must be realistically considered. Our bias against using bilateral ITA grafts during emergency operations during the period of this study was so strong that we excluded patients undergoing emergency surgery from analysis. Diabetic patients and women were less likely to receive 2 ITA grafts, but the differences were small (diabetic: bilateral ITA 11%, single ITA 13%; female: bilateral ITA 11%, single ITA 16%). Advanced age also had a negative correlation with the use of bilateral ITA grafts, based mainly on smaller numbers of patients over 70 years of age in the bilateral ITA group. Also, the use of 2 ITA grafts was not consistent throughout the time period of the study. Until approximately 1980 the use of 2 ITA grafts was limited to situations in which venous conduits were not available or for extremely young patients. Thus some patients in the bilateral ITA group have been followed

up for more than 20 years, but the median follow-up of the bilateral ITA group was just over 10 years, and fewer than 100 patients were followed for more than 13 years. Conclusions from this study are most valid for a 12-year time frame.

The ideal way to eliminate bias in the selection of treatment is to conduct a randomized clinical trial. Randomization should neutralize selection bias and allow comparison of treatment strategies for equal patient subsets. However, substantial difficulties are associated with the concept of a randomized trial comparing single ITA versus bilateral ITA grafting. The experience of the Coronary Artery Surgery Study (CASS) and the Bypass Surgery Angioplasty Revascularization Investigation (BARI) has taught us that selection bias is profound in randomized trials, but that selection bias is exerted at the point of inclusion into the trial rather than at the point of treatment choice. Expense is a major issue associated with these large trials, and even if funding and participants were available today, 10-year results would not be available for at least 15 years.

The standard of randomized clinical trials can be achieved only partially in nonrandomized comparisons. Coupling comparisons with traditional risk factor analysis adjusts for at least some factors related to selection so long as they also influence outcome. However, this gives rise to the question of confounding selection with outcome.

The most common method for obtaining comparable but nonrandomized groups has been by matching. Matching tends to be done on only a few variables, since matching on multiple variables quickly tends to fail to find suitable matches, and, therefore, neither maximizes the available pool of patients for comparison, nor extensively matches them. Further, if one matches on variables known to influence outcome, these variables tend not to be able to be used as adjustments in the comparison. In this study the method of matching was according to propensity score. The strength of matching using the propensity score is that it simultaneously matches on all known characteristics, allows all variables to be used as risk factors, and maximizes the use of patients. However, sometimes one finds subsets of patients that have either an extremely low or high propensity for one or the other arms of the comparison and cannot be used. Thus, in this study matching according to propensity score eliminated 3976 of the single ITA patients from the propensity-matched analyses because their propensity scores predicted they were poorly comparable with the bilateral ITA patients. Recently, the propensity score has been

incorporated into multivariable comparison analyses as a variable, as in our study, although its properties are debated.²⁷ This creates a hybrid model in which most of the values for variables in the model are from each individual patient, but also each patient has a variable whose score is determined by the general behavior of the overall group, namely, the propensity score. Importantly, this strategy does not produce a model that can be readily used for outcome prediction, as is true of traditional risk factor models. The limitation of all matching schemes, including propensity scores, is that the matching is done for known sources of selection bias, but cannot protect against unknown sources of selection bias, as do randomized trials.

In the hope of analyzing outcomes in ways that are both accurate and understandable, we have used multiple statistical strategies and have presented the results in multiple ways. Unadjusted late survival and reoperation-free survival curves for the entire patient sample are contained in Fig 1, and the unadjusted survival curves and reoperation hazard curves for the propensity-matched patients are in Fig 2. Unadjusted curves for the propensity-matched patients in regard to the risk factors of age, diabetes, and left ventricular function are contained in Figs 5, 6, and 7. We have generated traditional parsimonious risk factor models for the entire patient group (Table II), parsimonious models for propensity-matched patients (Tables V, VI, and VI), and nonparsimonious models maximally incorporating all available variables as well as their propensity scores (Table III). Each type of model has advantages and disadvantages. The use of parsimonious risk factor models enables the identification of multiple risk factors that affect outcome and allows the production of models that can be used for outcome prediction. For the overall comparison of the surgical strategy of 1 versus 2 ITA grafts, nonparsimonious models offer the most conservative and reliable estimates because all available variables including the propensity score are included. The bootstrap resampling adjustment of the estimates is an attempt to make the comparisons even more conservative.

Every comparison has shown better outcomes for patients with bilateral ITA grafts. Multiple statistical techniques have been used in efforts to reject the idea that bilateral ITA grafting produces superior outcomes to single ITA grafting, but all have failed. They all consistently point to a benefit of bilateral ITA grafting, and the more adjustments that are made for confounding, the more the increase in the estimated magnitude of the benefit of receiving 2 ITA grafts. The answer to the simple question, "Are 2 ITA grafts better than one?" is "Yes."

Substantial effort was made to quantify the extent of benefit of bilateral ITA grafting. Fig 4 illustrates the predicted distribution of outcome improvement over the first 12 postoperative years based on 1 versus 2 ITA grafts using multivariate techniques that included all patient information for the propensity-matched groups. Over that period, bilateral ITA grafting prevented reoperation more than it prevented death. For half of the patient sample, the improvement in the survival based on bilateral ITA grafting was predicted to be less than 6% (0.5% per year of follow-up).

For the practicing surgeon, identification of subgroups predicted to experience only small benefit from a more complex surgical technique is obviously useful. Traditionally important risk factors for late survival (age, diabetes, and left ventricular function) were examined to see whether these variables could be used to identify patients without major benefit. Bilateral ITA grafting achieved better survival regardless of left ventricular function and regardless of the presence or absence of treated diabetes. Young patients benefitted relatively little in terms of survival (over the first 12 postoperative years) but benefitted greatly from bilateral ITA grafting in the avoidance of reoperation and PTCA. No subgroups were identified that were predicted to have worse outcomes with bilateral ITA grafting.

Bilateral ITA grafting improves outcomes for patients at a high risk of an event. Patients at a high risk to die have better survival and patients at a high risk of reoperation and/or PTCA had fewer of these reinterventions. However, the variables that predict the composition of high and low benefit groups are multiple, as depicted in Figs 8 and 9.

It is also important to re-emphasize that this study basically deals with a 12-year postoperative follow-up interval. Some patients, particularly in the younger age group, do not have a substantial increase in their already favorable survival over 12 years, but there is no sign that the benefits of bilateral ITA grafting are lessening with time, and by 20 postoperative years the improvement in survival may be much greater.

We examined the details of surgical strategy (Appendix 2) in both univariate and multivariate settings. Any ITA-LAD graft decreased the risk of death, reoperation, and PTCA, and there was a slight but significant increase in the risk of reoperations for patients with an ITA-RCA graft. Other studies have also noted imperfect outcomes with RITA-RCA grafts.²⁸⁻³⁰ No other variations in the use of ITA grafts influenced outcomes. Examination of Appendix 2 will show some unusual grafting combinations that were usually based

on unusual situations of coronary anatomy, myocardial infarction in the distribution of one of the major vessels, or ITA size or anatomy, but also may have been related to relative surgical inexperience. Our current strategy is to use the ITA grafts to revascularize the most important left-sided vessels, sometimes as a composite LITA and RITA "Y" graft. This is a change in strategy relative to this series and is based in part on the emergence of other arterial grafts (right gastroepiploic artery and radial artery) that may be used as grafts to the RCA. Composite ITA grafting allows more options in the use of the free RITA but was not used during the years encompassed in the study. Thus, although this series may not reflect the ideal use of the ITAs in every case, it does reflect the results of what was the actual practice for a consecutive series of patients. It is also important to note that this is not a study of total arterial revascularization—the majority of patients received some vein grafts, a factor that may or may not have compromised outcomes. Today we are more adept at achieving total arterial revascularization, but whether that will improve outcomes is not known.

This study has produced different results than previous studies that have compared single and bilateral ITA grafting. The simplest possible explanation for this difference is that this study contains larger numbers of patients who received bilateral ITA grafts and they have been followed up for longer postoperative intervals. A study from Europe by Sergeant, Blackstone, and Meyns⁵ that investigated similar issues and contained large patient numbers showed no advantage for bilateral ITA grafting in regard to either survival or reoperation-free survival. However, although that study contained a large number of patients overall, the subset of patients who had undergone bilateral ITA grafting was much smaller and their mean postoperative follow-up interval was only approximately 6 years. Also, differences between the European and American medical milieus in the indications for primary bypass surgery and in the indications for reinterventions may influence outcomes. Smaller studies from United States centers have not shown significant survival differences, but many have shown either significant decreases in late cardiac events or trends in that direction associated with bilateral ITA grafting.^{6,8,12,13}

We do not believe that the implication of these data is that every patient undergoing bypass surgery must receive bilateral ITA grafts. Emergency operations and reoperations were excluded from this study, and few patients over 70 years of age were included. There was an increased risk of wound complications for diabetic patients, although that increase in risk was small.

Bilateral ITA grafting makes coronary surgery more complicated, and the results of this study must be evaluated with the realization that the surgeons involved were experienced in coronary surgery in general and in complex arterial grafting in particular. Concepts of coronary surgery continue to evolve, and the advent of radial artery grafts provides another choice for arterial revascularization, although the long-term effectiveness of radial artery grafts remains to be determined. Opponents of multiple arterial grafting strategies may argue that there were patients in our study for whom the incremental benefit of bilateral ITA grafting (at least over 12 years) may be small, particularly in terms of survival. Ultimately, for each bypass operation each individual surgeon must decide what operation that surgeon can accomplish for that patient at that time that will produce the best short- and long-term outcomes. Many factors must be considered.

However, until now it has been the position of some coronary artery surgeons that the consideration of multiple arterial grafting could be ignored because no clear evidence existed that outcomes were improved for any patient subsets. That position is no longer tenable. The data from this study indicate that the strategy of bilateral ITA grafting decreases the risk of death, reoperation, and PTCA when compared to a strategy of single ITA grafting.

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Discussion

Dr Hendrick B. Barner (*St Louis, Mo*). It is a pleasure to discuss this report, which I have long anticipated and which reflects surgical expertise and dedicated patient follow-up. It has been 12 years since the report of enhanced survival and reduced ischemic events when a single ITA is grafted to the LAD coronary artery. For a number of reasons, the logical step of showing an advantage for 2 ITAs over 1 ITA has been more arduous, but the dedication of the Cleveland Clinic surgeons has resulted in another landmark paper.

In most hearts, the LAD is the most important coronary artery, and it is self-evident that if 2 ITAs are to be proven better than 1 ITA, the second ITA must be placed to the next most important coronary artery in terms of the mass of viable myocardium subtended by that artery. By and large, the authors have achieved this goal, but not perfectly, since 7% of the single ITA grafts were placed to the diagonal artery or its equivalent, and in 13% of patients with bilateral ITA grafting, 1 ITA was placed to the diagonal artery or its equivalent. Thus 6% more of bilateral ITA patients had placement of 1 ITA to the diagonal artery, which was probably not the second most important coronary artery. Had it been placed to a more important coronary artery, this might have resulted in even better outcome for the bilateral ITA group.

The modest use of the ITA as a free graft is surprising considering the Cleveland Clinic was one of the first to report such use in 1973. As a consequence, the in situ RITA crossed the midline to reach the left side of the heart in 64% of patients. I believe your practice has been to bring it across anteriorly rather than through the transverse sinus, and you have reported relative success when some of these patients did require reoperation from the standpoint of injury to the anterior crossing RITA. In view of the favorable experience with routine use of the free RITA, as reported by Dr Tatoulis, has your practice in this regard changed in the last decade?

The incidence of diabetes was relatively high at 10.8% for the bilateral group and low at 13% for single ITA use. It is understandable that this incidence would be low in the bilateral group because of the risk of mediastinitis, but was it low in the single ITA group because of patient selection? This raises the issue of a selection by the surgeon, which is probably the greatest limitation of this study.

Dr Lytle. Let me address the statistical methods first. Two different statisticians used two different approaches to these analyses. Ms Houghtaling used Cox proportional hazard models of the entire group and selected subgroups, whereas Dr Blackstone used hazard function and interaction based analy-

ses. They ended up with almost identical conclusions. I am very comfortable with the statistical methods used in this study.

In regard to the vessels grafted with the ITA grafts: Although the LAD coronary artery is usually the most important anterior vessel, that is not always the case. In the single ITA group, 7% of patients received an ITA-diagonal graft, usually because the diagonal was the most important artery. These patients may have had a small LAD or a previous LAD infarct. For the bilateral ITA graft group, in 60% of patients the LAD and circumflex were the vessels receiving ITA grafts and in 20% it was the LAD and RCA. The hodgepodge of other combinations was usually reflective of unusual anatomic situations, a lack of LAD stenosis, or previous myocardial infarction. Remember, this was a consecutive series.

I share your concerns about patient selection and, indeed, the tendency to select good-risk patients for bilateral ITA grafting has always made it difficult to clearly demonstrate that surgical strategy produces better long-term outcomes. There is no question that there is a bias to select good-risk patients for extensive arterial grafting strategies. However, in

this study the baseline differences in the single and bilateral ITA groups in the prevalence of variables like diabetes, age, and female gender were relatively small. We attempted to adjust for those baseline differences with our statistical analyses. It is impossible to ever rule out completely the fact that the improved survival of the bilateral ITA group was not based on some good-risk patient-related characteristics that we did not identify and adjust for. However, although the risk of late death is less for good-risk patients, previous studies have clearly shown that the prevalence of late reoperation is greater for good-risk patients. The patients in the bilateral ITA group had both fewer late deaths and fewer late reoperations. Thus we cannot have it both ways. If we say that the patients in the bilateral ITA group were better risk patients, it would stand to reason that they should have had more reoperations rather than fewer reoperations. In my opinion, these data are suggestive that survival is improved with the bilateral ITA strategy compared with a single ITA graft, but I think that there is no question that the risk of reoperation is a lot less when 2 ITAs are used.

Appendix 1. Comparison of baseline variable between patients with bilateral ITAs (n = 2001) and patients with a single ITA and an SVG (n = 8123)

Factor square	2 ITAs: Frequency (%)	1 ITA ≥ 1 SVG: Frequency (%)	χ^2 P value
Gender			
Male	1786 (89.3)	6815 (83.9)	<.001
Female	215 (10.7)	1308 (16.1)	
Diabetes			
Yes	212 (10.8)	1052 (13.0)	.009
No	1750 (89.2)	7054 (87.0)	
History of smoking			
Yes	766 (42.9)	3102 (43.7)	.567
No	1019 (57.1)	4002 (56.3)	
History of myocardial infarction			
Yes	1029 (51.5)	4322 (53.3)	.139
No	970 (48.5)	3784 (46.7)	
Infarction according to electrocardiogram			
Yes	651 (32.6)	2560 (31.6)	.397
No	1348 (67.4)	5546 (68.4)	
Family history of coronary artery disease			
Yes	1129 (70.2)	4221 (66.8)	.008
No	479 (29.8)	2103 (33.2)	
Extent of disease			
Single	35 (1.8)	273 (3.4)	<.001
Double	526 (26.3)	2309 (28.4)	
Triple	1440 (72.0)	5540 (68.2)	
Left ventricular function			
None	730 (36.5)	2805 (34.5)	<.001
Mild	552 (27.6)	2059 (25.4)	
Moderate	277 (13.8)	1282 (15.8)	
Severe	442 (22.1)	1977 (24.3)	

Appendix 1. Continued

Factor square	2 ITAs: Frequency (%)	1 ITA ≥ 1 SVG: Frequency (%)	χ^2 P value
Left main disease			
Yes	269 (13.4)	1001 (12.3)	.175
No	1732 (86.6)	7122 (87.7)	
LAD ≥ 70% stenosis			
Yes	1663 (83.1)	7118 (87.6)	<.001
No	338 (16.9)	1005 (12.4)	
Peripheral vascular disease			
Yes	171 (8.6)	894 (11.0)	.001
No	1828 (91.4)	7212 (89.0)	
New York Heart Association functional class			
I	368 (18.4)	1260 (15.6)	<.001
II	714 (35.7)	2720 (33.5)	
III	213 (10.6)	811 (10.0)	
IV	706 (35.3)	3319 (40.9)	
Age (y)			
20-29	2 (0.1)	9 (0.1)	
30-39	93 (4.6)	221 (2.7)	
40-49	414 (20.7)	1335 (16.4)	
50-59	866 (43.3)	2957 (36.4)	
60-69	564 (28.2)	2708 (33.3)	
70-79	60 (3.0)	865 (10.7)	
80-89	2 (0.1)	28 (0.3)	

ITA, Internal thoracic artery; SVG, saphenous vein graft.

Appendix 2. Conduit and vessel data for bilateral ITA group (n = 2001)

Conduits/vessels	Frequency
LITA-LAD	651
RITA-Cx	121
RITA-Dg	98
RITA-RCA	314
RITA-Cx and Dg	1
RITA-LAD and Dg	2
Free RITA-Cx	55
Free RITA-Dg	10
Free RITA-RCA	47
Free RITA-Cx and Dg	2
Free RITA-LAD and Dg	1
LITA-Cx	1043
RITA-LAD	849
RITA-Dg	37
RITA-RCA	48
RITA-Cx	4
RITA-LAD and Dg	19
RITA-LAD and Cx	1
Free RITA-LAD	53
Free RITA-Dg	5
Free RITA-RCA	8
Free RITA-Cx	2
Free RITA-LAD and Dg	17
LITA-Dg	95
RITA-Cx	3
RITA-LAD	67
RITA-RCA	16
RITA-LAD and Dg	1
Free RITA-Cx	4
Free RITA-LAD	2
Free RITA-RCA	2
LITA-RCA	6
RITA-Cx	3
RITA-LAD	2
RITA-RCA	1

Appendix 2. Continued

Conduits/vessels	Frequency
LITA-LAD and Cx	3
RITA-Dg	1
RITA-LAD	1
Free RITA-Cx	1
LITA-LAD and Dg	181
RITA-Cx	63
RITA-LAD	1
RITA-Dg	3
RITA-RCA	81
RITA-Cx and Dg	1
Free RITA-Cx	18
Free RITA-RCA	13
Free RITA-Cx and RCA	1
LITA-Cx and Dg	6
RITA-LAD	4
Free RITA-LAD	2
LITA-Cx and RCA	1
RITA-Dg	1
Free LITA-LAD	3
RITA-Cx	1
Free RITA-Cx	2
Free LITA-Cx	7
RITA-LAD	1
Free RITA-LAD	5
Free RITA-RCA	1
Free LITA-RCA	1
RITA-LAD	1
Free LITA-Dg	3
RITA-LAD	2
Free RITA-LAD	1
Free LITA-LAD and Dg	1
RITA-RCA	1

LITA, Left internal thoracic artery; LAD, left anterior descending coronary artery; RITA, right internal thoracic artery; Cx, circumflex artery; Dg, diagonal branch; RCA, right coronary artery.

Appendix 3. Variables examined in multivariable analyses

Demography:

Sex, age (years), weight (kg), height (cm), body surface area (m²), body mass index

Symptoms of reversible ischemia:

Canadian heart class (1-4)

Left ventricular function:

Grade of left ventricular dysfunction (none = 1, mild = 2, moderate = 3, severe = 4), history of congestive heart failure, history of previous myocardial infarct

Cardiac comorbidity:

Family history of coronary artery disease

Noncardiac comorbidity:

History of smoking, peripheral vascular disease, chronic pulmonary disease, pharmacologically treated diabetes, treated hypertension

Coronary anatomy:

Left main disease (percent diameter reduction, presence of $\geq 50\%$ stenosis), LAD coronary system disease (percent maximal diameter reduction, presence of $\geq 50\%$ and $\geq 70\%$ stenosis), circumflex coronary artery system disease (percent maximal diameter reduction, presence of $\geq 50\%$ and $\geq 70\%$ stenosis), RCA system disease (percent maximal diameter reduction, presence of $\geq 50\%$ and $\geq 70\%$ stenosis), number of diseased systems ($\geq 50\%$ criteria)

Coronary operation:

Single versus bilateral use of ITA grafting, ITA to LAD, ITA to RCA, ITA to circumflex

Experience:

Date of operation (number of years since January 1971)

For propensity analysis only:

Surgeon

Appendix 4: Effectiveness of propensity score matching of patients within propensity quintiles 3, 4, and 5 for selected variables

Variable	Quintile*								
	3			4			5		
	BITA	SITA	P	BITA	SITA	P	BITA	SITA	P
N	110	1913		446	1570		1351	664	
Male (%)	82	79	.6	85	83	.2	93	89	.01
Age (y)	61 ± 8.2	60 ± 9.0	.2	59 ± 8.1	59 ± 8.4	.2	54 ± 8.1	56 ± 8.0	<.0001†
Weight (kg)	80 ± 13.4	80 ± 14.0	.98	82 ± 12.9	82 ± 13.8	.4	84 ± 13.5	83 ± 14.9	.5
Left ventricular function (1-4)	2.3 ± 1.16	2.3 ± 1.19	.98	2.3 ± 1.16	2.3 ± 1.20	.7	2.2 ± 1.16	2.2 ± 1.17	.3
Systems diseased (1-3)	2.6 ± 0.54	2.7 ± 0.52	.2	2.7 ± 0.50	2.7 ± 0.51	.96	2.7 ± 0.48	2.7 ± 0.52	.06
Diabetes (%)	11	16	.15	16	14	.3	9	11	.07
Ten-year survival	75 ± 4.5	74 ± 1.1	.4	81 ± 2.0	74 ± 1.2	.005	85 ± 1.0	77 ± 1.8	<.0001

BITA, Bilateral internal thoracic artery; SITA, single internal thoracic artery.

*The first two quintiles encompass only 68 patients with BITA grafts.

†Note: The difference in age is in the ninth decile (56 ± 8.0, n = 507, vs 57 ± 7.8 years, n = 501, $P = .01$), not in the extreme (tenth) decile (52 ± 7.8 years, n = 844, vs 53 ± 7.5 years, n = 163, $P = .5$).

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