SURGERY FOR ADULT CARDIOVASCULAR DISEASE

IS RETURN OF ANGINA AFTER CORONARY ARTERY BYPASS GRAFTING IMMUTABLE, CAN IT BE DELAYED, AND IS IT IMPORTANT?

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Background: Because survival after either an operation or angioplasty is similar across a wide spectrum of coronary patients, lasting symptom relief assumes high priority. **Objectives:** The objectives of this observational clinical study were (1) to determine whether the return of angina is immutable; (2) to identify factors that might delay its return, and (3) to evaluate whether its return is predictive of subsequent adverse events. **Methods:** The return of angina of any degree of severity and morbid events subsequent to its return were studied by multivariable time-related analyses in a consecutive series of 9600 patients who were undergoing primary isolated coronary bypass operations between 1971 and 1992. **Results:** The freedom rate from return of angina was 94%, 82%, 61% and 38% at 1, 5, 10, and 15 years. Increased modest risk of early return of angina was associated with preoperative demographic, symptom, coronary and vascular disease variables but reduced by more extensive arterial grafting. The ever-increasing risk of late return of angina was associated with demographic, symptomatic, left ventricular function, and coronary disease variables and was related strongly to comorbidity but was weakly reduced by controllable surgical variables. After the return of angina, 10-year freedom rate from infarct and survival was 71% and 68% respectively. **Conclusions:** (1) The risk of angina return increases relentlessly after operation, so it is likely immutable. (2) Delay of late angina return by use of arterial grafting is clinically trivial; control of noncardiac comorbidity may be more effective. (3) Fortunately, the return of angina after coronary artery bypass grafting has minimal impact on survival and is not predictive of imminent infarct. (J Thorac Cardiovasc Surg 1998;116:440-53)

Cardiac surgeons have migrated toward the use in coronary artery operation of multiple arterial grafts, including both internal thoracic (mammary) and gastroepiploic and radial arteries, under the assumption that, because a single arterial graft to the left anterior descending artery (LAD) improves

graft patency and late survival, multiple arterial grafts would amplify the effect. However, it has been difficult to demonstrate a survival benefit of multiple arterial grafts compared with a single one,¹ and a previous study failed to identify a late benefit of even a single arterial graft on return of ischemic

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symptoms.² Therefore we have studied the return of angina symptoms after coronary artery bypass grafting (CABG) in a larger patient population in which both single and multiple arterial grafting has been performed with follow-up to 20 years to determine (1) whether return of angina is immutable, (2) the factors, including grafting technique, that might delay its onset, and (3) whether its return is predictive of subsequent adverse events.

Methods

Patients. A consecutive series of 9600 patients underwent isolated first time CABG at the Gasthuisberg University Hospital of Leuven (Katholieke Universiteit Leuven) in Belgium from the start of CABG in 1971 until January 1992. Single coronary system disease was present in 11% of the patients, 2-system disease in 29% of the patients, and 3-system disease in 60% of the patients. The complete dataset has been described and characterized in detail in a previous publication.¹

Surgical technique. The number of conduits used was 1 (12%), 2 (42%), 3 (38%), 4 (7%), and 5 (1%). The number of distal anastomoses was 1 (9%), 2 (24%), 3 (31%), 4 (23%), 5 (10%), 6 (3%), 7 (1%), 8 (0.02%), 9 (0.02%), and 10 (0.01%).

The first internal thoracic artery (ITA) anastomosis was constructed in 1972, and 6074 patients had at least 1 in situ ITA anastomosis. The first bilateral in situ ITA graft ($N = 1192$) was used in 1973, and the first in situ sequential ITA graft ($N = 711$)³ was performed in 1978. Bilateral ITA grafts were connected to 2 different coronary systems in 985 patients and to only 1 single system in 207 patients. Free ITA grafting was used in 122 patients.

Follow-up. A regular stream of follow-up reports from referring specialists updates the Katholieke Universiteit Leuven Coronary Surgery Database.⁴ These reports are sent after each event, suspicion of event, or regular visit. In addition, a formal cross-sectional follow-up of known surviving patients was undertaken between January 1, 1993, and July 1, 1994.¹ The common closing date for outcomes information was set at 1 Jan 1993. The follow-up was complete for 99.9% of patients. The median follow-up for the survivors was 6.4 years. Table I gives the number of patients at risk by year after the operation (alive without having experienced the return of angina after CABG) and by number of in situ thoracic artery distal anastomoses.

Once complete follow-up was obtained, the dataset was refined for intervals without any information, for timeframes around and or immediately after important clinical events, reangiographies, and cardiologic or cardiosurgical reinterventions. This cascade of letters was organized and monitored with a follow-up management information system.

Events

Return of angina. The object of the study was the event defined as return of angina of any degree of severity without death or infarct the same day. The intent was to identify patients with return of reversible ischemia in contrast to those experiencing an acute myocardial infarction.

Table I. No. of patients at risk by year after operation (alive without having had return of angina after CABG) and by number of in situ thoracic artery distal anastomoses

Years after operation	No. of distal anastomoses				
	0	1	2	3	4
At operation	3526	4347	1542	182	3
1	3140	4037	1443	171	3
2	2946	3496	1060	123	2
3	2759	2882	799	103	2
4	2458	2370	689	95	2
5	2226	1923	507	72	1
6	2015	1523	373	42	0
7	1729	1214	250	13	
8	1419	946	176	6	
9	1112	751	119	5	
10	835	564	90	5	
11	544	406	81	5	
12	333	318	67	5	
13	246	214	49	4	
14	187	116	13	0	
15	140	65	0		
16	97	26			
17	45	13			
18	25	10			
19	5	5			
20	2	1			

Patients not experiencing this event were censored at the common closing date, at the end of follow-up for those with incomplete follow-up, or at death, whichever occurred earliest. The diagnosis of angina was documented, at the discretion of the attending cardiologists, with cyclo-ergometric or radionuclide tests and coronary angiograms. When these were found to be normal and when the clinical history left doubt, the chest pain was not coded as return of angina.

Events after the return of angina. Events studied after the return of angina were death, myocardial infarction, and reintervention (cardiologic or cardiosurgical). The time interval from the return of angina (time-zero) to the occurrence of these events was analyzed.

Characterization of overall freedom from angina. Non-parametric estimates of overall non-risk-adjusted freedom rate from angina were obtained by the method of Kaplan and Meier.⁵ A parametric method was used to resolve the number of hazard phases, to identify the form of the equation for each phase, and to estimate the parameters that characterized the distribution of times until first return of angina.⁶

Depictions. In various figures, events are depicted by a symbol positioned along the horizontal axis at the time of the event and on the vertical axis according to the Kaplan-Meier life table estimate. They are enclosed at periodic intervals between confidence limits equivalent to 1 standard error. The numbers in parentheses represent the number of patients without the event and traced

Table II. *Patient-profile of the median patient used for the nomograms and patient-specific predictions*

Demographics	Age	58 yr
	Gender	Male
Reversible ischemia	Anginal class	2
	Operation	Elective
	Exercise test	Angina
	Exercise test	Electrocardiographic changes
Myocardial infarction	Anterior infarct	Absent
	Septal infarct	Absent
Left ventricular function	Left ventricular hypertrophy	Absent
Coronary disease	System disease	3
	Left main stenosis	Absent
Coexisting cardiac	Aortic valve stenosis	Absent
Coexisting vascular	History of peripheral vascular disease	Absent
	History of vascular operation	Absent
	Calcified ascending aorta	Absent
Coexisting noncardiac	Diabetes of any grade	Absent
	Current or previous obesity	Absent
	Hypertension	Absent
	Renal failure history	Absent
Hyperlipidemia	Triglyceride level	165 mg/dl
Procedural variables	Graft to the LAD	Present
	No venous graft to LAD	
	ITA grafts as conduits	Not only
	Venous grafts as conduits	Not only
	Patch grafting	Absent
	Coronary endarterectomy	Absent
	No vessels of ≤ 1 mm	
	Anastomosed	
	Revascularization	Complete
	Distal anastomoses	3
	Distal arterial anastomosis	1
Procedural variables	High risk for return of angina surgeon	No
	Low risk for return of angina surgeon	No
	Year of operation	1991

beyond that point. When parametric time-related depictions are shown, the solid line is the parametric estimate of freedom from the event enclosed within dashed 70% confidence limits equivalent to one standard error.

Multivariable analysis of return of angina. The general methods used to identify incremental risk factors for return of angina have been described previously for the event death,¹ including the variables and their organization for analysis and the exploratory analyses accompanying the multivariable analyses conducted in the parametric, multiphase hazard function domain.

In the directed stepwise entry of variables into the multivariable risk factor model, the *P*-value criterion for retention of variables in the final analysis was .05. Regression coefficients are presented ± 1 standard error.

Sequential analyses. To better understand the nature and influence of the risk factors, the multivariable analysis was conducted in a sequential fashion. First, only patient variables were entered, then procedure variables that were likely to be known or estimated at the time of decision-making were added, including the use and method of use of arterial grafts, and finally experience variables were entered. Variables from the isolated and preceding analyses were allowed to leave the model.

Nature and influence of risk factors. Nomograms representing the solution of the patient, procedure, and experience parametric equation for specific supplied values of each factor were used to explore the influence of risk factors. In general, each figure represents the prediction for a specific but typical hypothetical patient (Table II) whose profile was the median for patients who underwent an operation in the last year of entry into the study. Point estimates are enclosed within confidence limits equivalent to ± 1 SE. However, for statistical consistency, the solid lines for comparative difference in predicted percent freedom from angina are enclosed within dashed 90% confidence limits.

Results

Freedom from the return of angina after CABG.

The non-risk adjusted 1-, 5-, 10-, and 15-year freedom rate from angina of any degree of severity, without infarct or death on the same day, was 94%, 82%, 61%, and 38%, respectively (Fig. 1, *A*). A 2-phase hazard function (Fig. 1, *B*) was identified. It consisted of a small early hazard phase that was slowly declining and a prominent late hazard phase

Fig. 1. A, Parametric freedom from the return of angina, without death or infarct the same day, after primary isolated CABG ($n = 9600$). B, Hazard function for the return of angina, without death or infarct the same day, at any time after primary isolated CABG ($n = 9600$; instantaneous risk at every point in time after the operation).

that was continuing to rise relentlessly after approximately 2 years for the extent of the follow-up. The implication is that if a patient lives long enough, angina will return (is immutable).

In most instances, the return of angina was of mild severity (Table III).

Influence of choice of conduit on the return of angina after CABG

Risk unadjusted influence. Choice of arterial grafting compared with the choice of all vein grafts was associated with a lower risk—unadjusted prevalence of the return of angina after CABG (Fig. 2, A; $P =$

Table III. The grade of angina at first return

Angina class	N	%
Class I	1535	58.8
Class II	876	33.5
Class III	142	5.4
Class IV	59	2.3
TOTAL	2612	100

.0001). Stratification by number of in situ ITA anastomoses identified no apparent additional benefit of multiple arterial grafting before risk adjustment (Fig. 2, B).

Fig. 2. A, Actuarial freedom from angina after primary CABG, by presence or absence of arterial grafting (combined or not with nonarterial grafting). B, Actuarial freedom from angina after primary CABG, by 1 or more than 1 in situ thoracic artery (IMA) distal anastomoses.

Risk adjusted influence. Choice of arterial grafting (by in situ ITA, free ITA, or gastroepiploic artery) reduced the prevalence of anginal events after CABG, both in early and late phases, after adjustment for demographic and patient variability (Table IV). Fig. 3 depicts this benefit for a median patient (Table II). For that patient, the benefit of arterial grafting is approximately 5% at 10 years. An additional benefit was an increasing ratio of arterial to total number of distal anastomoses, corresponding to an increase in the number of arterial grafts used (Fig. 4). The benefit of extensive arterial grafting disappeared by 24 months after CABG.

Influence of immutable and only possibly controllable risk factors. Immutable demographic variables of younger age and of female gender were associated with both increased early and late return of angina (Table IV). For a 55-year-old median-risk patient (Table II) compared with a 75-year-old median-risk patient, the difference in freedom rate from angina was 10%. For a median-risk woman compared with a median-risk man, this difference at 10 years was 13%.

Noncardiac nonvascular comorbidities were potent risk factors for late the return of angina after CABG. At 10 years after an operation, the freedom

Table IV. Incremental risk factors and the P values, based on patient, procedure, and institutional variables, for the return of angina, without infarct or death the same day, after primary isolated CABG (see Appendix 2 for the selected variables, their coefficients, their standard error and their mathematic transformations)

Variables	Hazard phase (P value)	
	Early	Late
Patient		
Demographic		
Younger		
Age	<.0001	<.0001
Female	<.0001	<.0001
Anginal status		
Longer		
Duration of angina history	<.0001	<.0001
Higher		
Angina class		<.0001
Unstable ST-segment at operation	<.0001	
Clinically positive cycloergometric test and	.02	
Electrocardiogram negative exercise test (interaction)	.001	
Left ventricular function		
Absence		
Preoperative anterior or septal infarct		.01
Coronary disease distribution		
Lesser		
Stenosis of left main coronary artery	.002	.002
Multi-system coronary artery disease		.006
Comorbidity (cardiac)		
Left ventricular hypertrophy		.01
Aortic valve stenosis (mild)		.02
Comorbidity (vascular)		
History of peripheral vascular disease	.0001	
History of non-carotid vascular operation		.0008
Calcified ascending aorta		.01
Comorbidity (noncardiac, nonvascular)		
Hypertensive		.0007
Higher		
Diabetic grade		.0004
Absence		
Overweight now or previously and		.01
Age (interaction)		.003
Higher		
Preoperative triglyceride level		.0007
History of renal failure		.0001
Procedure		
Details of the conduit used		
Nonuse of vein grafts only	.02	
Use of vein grafts to the LAD system		.003
Use of patch grafts	<.0001	
Details of the distal anastomoses		
Proportion of total distal anastomoses to anastomosed vessels	.0009	
≤1 mm		
Nongrafting to the LAD	.01	
Ratio of the no. of arterial anastomoses to total no. of distal anastomoses	.0003	
Completeness of revascularization		
Incomplete revascularization and	<.0001	
Use of internal thoracic artery grafts only (interaction)	.01	
Other surgical details		
No. of coronary endarterectomies	.0004	
Institutional		
Surgeons		
High risk for angina return surgeon	.001	
Low risk for angina return surgeon	.007	
Experience		
Later		
Date of operation		<.0001

Fig. 3. Patient-specific prediction for a median patient (see Table II) validating the influence of the use of at least a single thoracic artery (IMA) anastomosis, preferably to the LAD, on the freedom from angina after CABG.

Fig. 4. Patient-specific prediction for a median patient (see Table II) validating the influence of increasing the ratio of arterial to total anastomoses on the freedom from angina after CABG. A ratio of 0:3 means that no arterial distal anastomosis was constructed on a total of 3 distal anastomoses. A ratio of 3:3 means that 3 arterial distal anastomoses were constructed on a total of 3 distal anastomoses. Note that the horizontal time axis is limited to the first 12 months.

rate from angina was 35% for a median-risk patient (Table II) with insulin-treated diabetes, 44% for a patient with orally treated diabetes, and 45% for a hypertensive patient, compared with 51% for a patient without these comorbidities.

Events after the return of angina

Death. The parametric non-risk-adjusted 1-month and 10-year survival was 99% and 68% after the return of angina after CABG (Fig. 5, A). Uncorrected for patient and procedure variability, this survival rate was

Fig. 5. A, The actuarial and superimposed parametric survival function after the first return of angina after CABG (time 0, the moment of return of angina). B, Actuarial survival function (uncorrected for patient-variability) after the first return of angina after CABG (time 0, the moment of return of angina), stratified by patients with a single ITA (*IMA*) anastomosis versus patients with more than a single ITA anastomosis. C, The actuarial survival function (uncorrected for patient variability) after the first return of angina after CABG (time 0, the moment of return of angina) stratified by the grade of angina at first return of angina (see Table III).

improved in the presence of an arterial graft ($P = .0001$). No additional reduction was identified by increasing the number of in situ thoracic artery anastomoses beyond a single one ($P = .8$) (Fig. 5, B). The more severe was the degree of angina at return, the worse was the subsequent survival rate ($P = .0001$). The 1-year survival rate was 80% when angina returned in the form of unstable angina and was 97% when the angina was mild (Fig. 5, C).

Myocardial infarction. The parametric 1-month and 10-year non-risk-adjusted freedom rate from infarct (Fig. 6, A) after the return of angina after CABG was 97% and 71%. Uncorrected for patient variability, freedom from infarct was strongly less ($P = .0001$) (Fig. 6, B) in the presence of an arterial

graft. No additional reduction was identified in the presence of a larger number of in situ ITA anastomoses at the time of the original procedure ($P = .17$). The higher the severity grade of angina was at return, the more frequent (earlier) was the occurrence of an infarct ($P = .0001$) (Fig. 6, C).

Reintervention. The parametric 1-month and 10-year non-risk-adjusted freedom rate from any cardiologic or cardiosurgical reintervention (Fig. 7) after return of angina after CABG was 96% and 59%.

Discussion

Limitations of the study

Intensity biases. The return of angina is a clinical event, based on careful interpretation of medical

Fig. 6. A, The actuarial and superimposed parametric freedom from infarct after the first return of angina after CABG (time 0, the moment of return of angina). B, The actuarial freedom from infarct (uncorrected for patient variability) after the first return of angina after CABG (time 0, the moment of return of angina), stratified by the presence of an arterial graft. C, The actuarial freedom rate from infarct (uncorrected for patient variability) after the first return of angina after CABG (time 0, the moment of return of angina) stratified by the grade of angina at the first return of angina (see Table III).

history, and therefore subject to possible bias. The first symptoms of the return of angina after CABG were most frequently of mild grade. Some may argue that the return or development of severe angina would have been a more discriminating end point. However, that presupposes a prognostic importance of the return of angina commensurate with its grade of severity. We chose not to take this approach but instead to study all grades of return of symptoms and to evaluate their prognostic importance.

Follow-up biases. Variable intensity of follow-up may have influenced the identification of the event. Medical care in Belgium is without financial consequences for the patient. It is possible that patients with considerable comorbidity have been subjected to more frequent follow-up. This is true for patients

who are treated with dialysis or insulin. This difference in follow-up intensity could produce a biased association between these comorbidities and the event, certainly for mild grades of angina. A reverse bias is equally possible, where patients who have been symptom-free for years will visit their cardiologist at the first symptoms of chest pain, sometimes indistinguishable from muscular pains, even for experts.

Unavoidable under-reporting. Under-reporting of the event may have occurred from silent ischemia.

However, the combination of a continuous clinical event update system and periodic formal follow-up constitutes the potential power of this database for the analysis of a refined event such as the return of angina. Most returns of symptoms were already documented in the database before the

Fig. 7. The actuarial and superimposed parametric freedom rates from any cardiologic or cardiosurgical reintervention (time 0, the moment of first return of angina).

formal follow-up and were based on the original documents of the attending cardiologists, documented a few days after the actual return. The additional cascade of letters further refined this information for the other patients. A follow-up study⁷ that used alternative follow-up methods (anniversary method) of patients with CABG with only venous grafts reported a similar freedom from angina as this study for patients with only venous grafts.

Limitations of the analytic method. A multivariable analysis comes closest to adjusting for the deliberate or unconscious patient selection in the variability of surgical techniques used. The complexity of the variables induce complex analyses, but they can generate patient-specific estimates useful for predictions. The strengths and limitations of these predictions on independent patient samples⁸ include: patients with new risks, variables unavailable for the analysis, variables with low numbers of patients at risk and therefore instability of the coefficients, and variables that have taken different meanings over time.

Deliberately imposed limitations. This study has been limited, by purpose, to the variables known before or at the time of surgery to permit prediction before the operation, even though the Katholieke Universiteit Leuven database contained time-related co-variables such as smoking habit and lipid values after the operation.

The impact of choice of procedure on the return of angina. The one completely controllable risk factor for the return of angina is the surgeon's choice of conduit for the operation. However, the benefit that can be anticipated in delaying the onset of angina by the use of extensive arterial grafting was found to be disappointingly small.

An earlier analysis² on a smaller data-set ($n = 5880$) with a shorter follow-up did not identify a beneficial effect on return of clinical ischemia of extensive arterial grafting over and above that afforded by a single arterial anastomosis. We speculated⁹ that, were the data-set larger and the follow-up longer, a progressive benefit of more extensive arterial grafting in reducing the early return of angina might be identified but that it was unlikely to reduce the clinically more important late return of angina.

Table V, a univariate and non-time-related presentation, suggests a benefit of the extensiveness of the arterial reconstruction, but this is before a correction for patient variability and method of use of this arterial grafting over time. Thus, in the present study with risk-adjustment, we found a progressive benefit on prevention of the early return of angina by more extensive arterial grafting, but the magnitude of this advantage was so small that the clinical benefit is trivial. Arterial grafting effected a small reduction in the late return of angina, but no incremental benefit of more extensive arterial grafting.

Table V. *The univariate non-time-related comparison of the no. of events within the follow-up interval by no. of in situ thoracic artery distal anastomoses (P [χ^2] = .001)*

No. of events	No. of distal anastomoses				
	0	1	2	3	4
Total N	3526	4347	1542	182	3
Return of angina (N)	1310	1025	253	24	0
TOTAL (%)	37.1	23.6	16.4	13.2	0

It remains possible for more extensive or complete arterial grafting to reduce very late clinical events (eg, 10 to 15 years after CABG), but a series of critical observations are appropriate. In our study, at 10 or 15 years after an operation only 61% and 38% of the surviving patients are at risk for the return of angina. With the mean age of the current CABG patient above 70 years at the time of surgery and his combination of co-morbidity, only a small segment of the current population could benefit from this possible residual hazard reduction. Also, because the late phase becomes dominant beyond 2 years after the operation, any substantial benefit of multiple arterial grafting should have become apparent. It did not, leading to the inference that the benefit must be small.

This disappointing finding follows on the heels of a similar disappointing¹ benefit of extensive arterial revascularization on early, late, and very late survival after CABG. Although that analysis identified neither increased nor decreased early risk with the use of either single or extensive thoracic artery grafting, it failed to identify reduced late risk by extensive arterial grafting. Even the benefit of single arterial in situ grafting was modest and vanished when severe comorbidity was present. This demonstrated that extensive data exploration is needed before statements can be made in situations where patient-mix can influence the results of operative strategy.

In addition to the choice of procedure, the other controllable factors are the surgeon and the environment. In our study, institutional variables identified as risk factors for the return of angina included the identification of 2 surgeons and variables describing their experience or their surgical protocols. These differences appeared only early. The magnitude of the differences at 1 month and 10 years after surgery between the 2 extremes of surgeons after normalization for patient and procedure variables

are limited to 0.2% and 2%, respectively, and therefore not clinically important.

The impact of demography and comorbidity on the return of angina. The therapeutic environment of the patient with coronary disease is constantly changing. The patient-mix of the larger cardiac operation centers includes patients with impressive accumulations of cardiac and noncardiac co-morbidities. Immutable demography and co-morbidity were associated with the earlier return of angina. Improved cardiac drugs and interventional techniques are rightfully challenging coronary operations in parts of the coronary patient-spectrum and for some of the follow-up events. The optimization of medical decision making in patient-specific situations¹⁰ and for different follow-up events requires updates of the scientific bases and optimal correction for the patient variability.

In addition to the vascular co-morbidity variables (calcified aorta, vascular disease, and vascular surgery), expressing the extent of the atherosclerotic process, a large late impact was identified in the variables related to the initiation and progress of this atherosclerotic process (hypertension,¹¹ diabetic grade, renal failure, triglyceride value). Preoperative triglyceride values were already previously identified as incremental risk factors for several outcome events after CABG: survival,¹ return of angina,^{2, 12} first infarct,² any first ischemic event.² These variables demonstrate the progressive nature of the atherosclerotic process that cannot be expected to be stopped at the time of operation. Aggressive medical treatment^{13, 14} and dietary regimens may interfere with these negative influences.

Clinical relevance of the return of angina after CABG for the patient. If the return of angina after a coronary operation is largely immutable, the choice of operative technique will delay its onset only mildly, and it is yet uncertain whether risk-factor intervention will be effective, it is fortunate that the return of angina appears to have limited consequence on survival. It is also only a modest predictor of impending infarct because only 3% of the patients will have an infarct the first month after the return of angina. The surgical or cardiologic reintervention rate after the return of angina was only 4% the first month, increasing within the first year to approximately 20%, then stabilizing after that interval. We have previously shown that survival after the return of angina is no different from that expected had angina not returned.² Whether a biologic or iatrogenic factor, reintervention is less

common after the return of angina when multiple arterial grafting has been performed. The return of angina is therefore an event with possibly high emotional impact on the until-then symptom-free patient, but its clinical consequences seem limited.

Inferences relevant to minimally invasive direct coronary artery bypass surgery. Minimally invasive direct coronary artery bypass (MIDCAB) surgery results refer nearly always to aggregate results of groups of patients treated with more conventional CABG techniques. The extreme patient selection for these lesser invasive techniques requires more precise standards for comparison. A patient-specific prediction was made for the return of angina in a typical patient with a median-risk profile who has undergone MIDCAB; the prediction is further refined with minimal co-morbidity, stable angina, single vessel disease, and an ITA anastomosis to the LAD. The 1-month, 5-year, and 10-year freedom rate from angina for this typical patient who has undergone MIDCAB was 99.8%, 86%, and 59%, respectively. We believe this should be the standard of comparison for such procedures.

Clinical inferences. The study demonstrates that most patients, if they live long enough, will experience the return of angina, most frequently of a minor grade, within 15 to 20 years after their CABG. Thus the return of angina appears to be immutable after a coronary artery operation. Patients should not expect that use of multiple arterial grafts will lead to dramatic reduction in the occurrence of this event beyond the modest benefit afforded by a single arterial graft to the diseased LAD. Demographic variables are immutable, and coronary atherosclerosis is a chronic disease that has been in evolution in these patients for many years and has reached the level of hemodynamic and clinical significance. Coronary operations will not stop this process. However progression of disease can be delayed, theoretically, by the control of noncardiac comorbidity. Finally, the tendency, for whatever reasons, to avoid re-intervention when arterial grafting is extensive appears to be prudent.

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Discussion

Dr. Bruce W. Lytle (Cleveland, Ohio). This is a follow-up of over 9000 patients undergoing operations for coronary bypass grafting, and it has a lot of strengths. The most important of these strengths is a 99.9% follow-up and a pattern of follow-up that is relatively continuous. These points are based on a very high degree of geographic localization of the patients involved and is a tribute to the tenacity of the investigators.

These data have been subjected to sophisticated and multi-directional statistical analyses. I am not going to ask any questions about Dr. Blackstone's methods because it

is unlikely that I am capable of understanding the answers. But I do think that we need to examine the endpoint.

Most studies of bypass operations focus on death and reoperation, because these events are not subjective and they have obvious clinical importance. My understanding is that first return of angina was a clinical diagnosis made by a referring cardiologist. Not only was it a subjective diagnosis, but the angina that occurred could have been an isolated event followed by a relatively benign clinical course. Do you have any data or any feelings about the data about the importance of a first-return-of-angina event in terms of predicting subsequent bad outcomes for the patient, death, reoperation, or disabling angina?

A second line of inquiry has to do with the business about arterial grafting. It does not appear that the strategy of complex arterial grafting had a major impact on the late return of angina, or whatever this event is. Now, we do need to realize that despite the 20-year extent of the study, the median follow-up was about 6 years, and only 128 patients with more than 1 internal thoracic artery anastomosis were followed for more than 10 years. So in reference to complex arterial grafting, this is really a study of the first decade after bypass operation.

I think the sensitivity of the event also has to be considered, because any time there are events that are extremely sensitive, they tend to blur the distinction among methods of treatment.

Furthermore, I would bet there was a very close covariance between young age, which is a very strong predictor of the recurrence of angina, and complex arterial grafting. Do you think you are able to perfectly isolate the effect of those very closely related variables even with multivariate techniques?

What implications do you think this study has in terms of your own practice in regard to the strategies of complex arterial grafting?

Lastly, interpreting the overall results, we can take solace from the sensitive nature of this endpoint. The fact that at the end of 20 years over 20% of the surviving patients had not had even a single event that some cardiologists might think was angina is, I think, remarkable.

Dr. Sergeant. First return of angina, is it a good outcome marker? First return of angina is a very sensitive marker. One day of angina, as you have pointed out, will have the event-flag go down and stay down forever.

This event was identified by the attending cardiologists or by the 2 senior researchers involved and mentioned as authors. A lot of effort was invested in the identification and refinement of the actual first return of angina.

Is it an important marker? We think it is an important marker. Even though it is sensitive, it is an important marker because it is the prime marker on the quality of life after coronary bypass operation. The uncertainty for the patient of the first return of angina is very destabilizing.

Is it an important marker for the late outcome? This is beyond the scope of this actual presentation, but we have explored this domain already in a previous analysis of the same event for a smaller dataset. This exploration indicated that the patients with return of angina, without

infarct or death the same day, have a similar survival rate to the patients without this event.

There are 2 possible explanations: either the first return of angina is not a good outcome marker, or we have been treating these patients perfectly, no overtreatment nor undertreatment. I would doubt this last possibility very much. I would therefore propose that it does not seem to be a good outcome marker.

Dr. Lytle is referring to Table I in the article when he mentions arterial grafting and the extent of follow-up, and it has to be noted that this is just a listing of each individual use of arterial grafts. Please note that the late-hazard phase starts to rise by 2 years. At 5 years in follow-up, there are 2269 patients with a single thoracic artery, and there are 609 patients with a double thoracic artery. These are only the in situ thoracic artery reconstructions; free and other arterial grafts need to be added to get a complete overview of extensive arterial grafting in this dataset.

The median follow-up duration is very much related to the entry of patients into the study. A completely uniform entry of patients over 20 years would optimize this median follow-up to 10 years maximum. The only possible inference of the median follow-up is that it reflects nonuniform entry of patients and the growth of our cardiac surgical program.

Younger age very strongly influences the return of angina. But as you have seen on the depictions, younger age does not interact significantly with arterial grafting. Extensive analysis was done into this relationship, and no additional interaction could be identified.

In the presentation in Prague¹ (EACTS 96), the benefit of extensive arterial grafting on survival was studied. There was no overwhelming benefit, even of the use of a single thoracic artery, and absolutely no benefit (once the patient variables were completely corrected for) in extending the use of arterial grafting.

We are therefore at this moment in time still using more extensive arterial revascularization but not going toward the extreme. The possible benefit on any event of radial and gastroepiploic artery grafting seems very distant if not unreachable, if the second thoracic artery benefit is so parsimonious. If there is no contraindication for the second thoracic artery, there seems to be no reason not to use it.

Appendixes

Appendix 1. Estimates for final model parameters (patient, procedure, and institutional variables):

Early phase: $d = 0$; $r = 1.053$; $n = 0$; $M = 1$

Late phase: $t = 1$; $g = 2.089$; $a = 1$; $h = 1$

Appendix 2. The selected variables, their coefficients, their standard error and their mathematic transformations for the final model (patient, procedure, and institutional variables):

Early phase: intercept = -3.980

Younger age ($[age\ (years)/50]^2$, squared transformation) = -0.5386 ± 0.122 ; female gender = 0.7586 ± 0.103 ; longer duration of angina history ($\ln[duration\ (months)]$ natural logarithmic transformation) = 0.1524 ± 0.033 ; unstable ST-segment at surgery = 0.5267 ± 0.086 ; clinically positive exercise test = 0.3942 ± 0.166 , and electro-

cardiogram negative exercise test = 9.5794 ± 9.180 (subgroup of patients experiencing onset of angina during exercise testing before electrocardiographic changes are evident); greater stenosis of left main coronary artery ($[\% \text{ stenosis}/100]^2$, squared transformation) = -9.8522 ± 9.27 ; history of peripheral vascular disease = 0.6062 ± 0.116 ; use of vein grafts only = -0.5739 ± 0.24 ; use of patch grafts = 0.1325 ± 0.28 ; proportion of total distal anastomoses to vessels of size 1 mm or less = 0.6602 ± 0.2 ; grafting to the LAD system = -0.3436 ± 0.133 ; lower ratio of the number of arterial anastomoses to total number of distal anastomoses ($1/\text{ratio} + 0.5$) inverse transformation) = 0.9393 ± 0.26 ; incomplete revascularisation = 0.4976 ± 0.108 and use of internal thoracic grafts only = 0.74 ± 0.3 (subset of patients who were incompletely revascularized, and only internal thoracic arterial grafts were used); number of coronary endarterectomies = 0.4937 ± 0.14 ; high risk for angina return surgeon = 0.3485 ± 0.106 ; low risk for angina return surgeon = -0.3052 ± 0.113

Late phase: intercept = -6.550

Younger age ($\ln(\text{years})$ logarithmic transformation) = -0.9071 ± 0.2 ; female gender = 0.3304 ± 0.072 ; longer duration of angina history ($\ln[\text{duration}(\text{months})]$ natural logarithmic transformation) = 0.3304 ± 0.072 ; higher angina class ($\ln[\text{angina class} + 1]$ natural logarithmic transformation) = 0.3414 ± 0.062 ; preoperative anterior or septal infarct = -0.2570 ± 0.102 ; greater stenosis of left main coronary artery ($[\% \text{ stenosis}/100]$ scaling transfor-

mation) = -0.2364 ± 0.099 ; multi-system coronary artery disease (2 or more systems diseased by 70% diameter reduction criterion) = 0.2291 ± 0.083 ; mild aortic valve stenosis = 0.4595 ± 0.2 ; left ventricular hypertrophy (by electrocardiographic criteria) = 0.2144 ± 0.085 ; history of non-carotid vascular surgery = 0.5204 ± 0.155 ; calcified ascending aorta = 0.7202 ± 0.3 ; overweight now or previously (more than 10 kg over ideal weight: for male patients, ideal weight is $[\text{height}(\text{cm})-100]$, and for female patients, ideal weight is $[\text{height}(\text{cm})-110]$) = -0.8918 ± 0.34 and older age (product of age [years] and obesity indicator variable [interaction term]) = 0.01818 ± 0.0062 ; hypertensive (defined as a systolic blood pressure greater than 160 mm Hg, a diastolic blood pressure greater than 100 mm Hg, or being medicated for hypertension by history) = 0.01748 ± 0.052 ; higher diabetic grade (grade 0, no diabetes; grade 1, abnormal glucose tolerance test with dietary treatment; grade 2, diabetic, receiving oral hypoglycemic treatment; grade 3, insulin-treated diabetes. The squared transform of diabetic grade is used.) = 0.05179 ± 0.0146 ; higher preoperative triglyceride level ($\ln[\text{triglyceride level}(\text{mg/dl})]$ logarithmic transformation) = 0.1818 ± 0.054 ; history of renal failure (patients receiving dialysis therapy or having received renal transplantation) = 1.218 ± 0.31 ; use of vein grafts to the LAD system = 0.1517 ± 0.051 ; later date of operation ($[\text{date}/13]^2$ squared, scaled transformation of date of operation expressed as the number of years between January 1, 1971, and the calendar date of the operation) = 0.3458 ± 0.067