

Recurrence of Angina After Coronary Artery Bypass Surgery: Predictors and Prognosis (CASS Registry)

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Objectives. This study sought to define the predictors and prognosis of postoperative angina in patients undergoing coronary artery bypass surgery.

Background. Angina recurs in the first postoperative year in 20% to 30% of patients after coronary artery bypass surgery. The Coronary Artery Surgery Study Registry provides an opportunity to study the predictors and prognosis of postoperative angina in a large sample.

Methods. All patients with isolated coronary artery bypass surgery in the registry were identified, and anginal status was determined on a yearly basis. The influence of angina on mortality, recurrent myocardial infarction and need for reoperation was determined.

Results. Angina recurred in the first year in 24% of patients and by the sixth year in 40%. The significant predictors in a multivariate analysis were minimal coronary artery disease, preoperative angina, use of vein grafts only, previous myocardial infarction,

incomplete revascularization, female gender, smoking and younger age. In subsequent years important predictors were angina in the first postoperative year, female gender, younger age and incomplete revascularization. The presence of angina in the first postoperative year was associated with more frequent myocardial infarction ($p = 0.04$) and greater need for reoperation ($p = 0.003$) but did not affect survival during the 6-year follow-up period.

Conclusions. These findings show that the predictors of postoperative angina are features that are or could be predicted before bypass surgery. Thus, patients with these features before bypass surgery could be advised that they would be more likely to experience postoperative angina than those without these features. Postoperative angina is associated with an increased risk of late myocardial infarction and reoperation.

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Angina pectoris occurring after aortocoronary artery bypass surgery is particularly discouraging because this symptom is the most frequent indication for coronary artery bypass surgery. Recurrence of angina in the first year alone has been reported in 20% to 30% (1,2) of patients undergoing bypass surgery. It is unclear whether angina after bypass surgery has the same prognostic implications for survival or has the same predictive value for future myocardial infarctions or need for coronary artery bypass surgery as occurs in unoperated patients with angina.

The Coronary Artery Surgery Study (CASS) Registry provides an opportunity to evaluate the prevalence, predictive factors and prognosis of angina occurring after bypass surgery

at 15 participating centers during a 4- to 8-year follow-up period.

Methods

Patients. From the CASS Registry of 24,958 patients, the 9,557 patients who underwent coronary artery bypass surgery without other associated cardiac surgery within 3 years were identified. In the present study, only patients with independent grafts to a single anastomotic site were included. Excluded were patients undergoing reoperation ($n = 242$), patients with congenital anomalies of the coronary arteries ($n = 47$) and patients with double ($n = 22$) or sequential ($n = 21$) internal thoracic artery grafts and Y ($n = 439$) or sequential ($n = 2,236$) saphenous vein grafts. Two study groups were defined: one for analysis of the predictors of angina and the second for analysis of prognosis of angina after coronary artery bypass surgery.

Follow-up. Follow-up for CASS Registry patients was done at annual intervals after enrollment angiography, so that the first follow-up after bypass surgery could have occurred any time within the first postoperative year. For the analysis of predictors of angina after coronary artery bypass surgery, the study group included 5,289 patients who were alive and had follow-up 1 year after bypass surgery, plus or minus 90 days.

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The 90-day window was also used in analyzing angina at 2 and 3 years postoperatively. The analysis of the relation of angina to survival and to the incidence of reoperation and myocardial infarction included 6,158 patients who had a follow-up visit at any time within 1 year after bypass surgery plus 90 days. Time to event data were dated from the day of bypass surgery. Annual follow-up was accomplished by mail and telephone interviews according to CASS protocol (3) for up to 8 years (mean 5.5 years).

Angina. At baseline and at each annual follow-up visit, the presence of chest pain was determined according to standardized protocol (3) and defined as *definite, probable, probably not,* and *definitely not angina*. For the present study, patients classified as having definite or probable angina were considered to have angina. When the analysis was repeated including only patients classified as having definite angina, the same results were obtained.

Cigarette smoking status was determined at baseline. Cigarette smokers were those smoking more than one-half pack per week. Current smokers included those smoking within the previous 3 months. *History of diabetes* included all diabetic patients, insulin dependent and non-insulin dependent. *Incomplete revascularization* was present when a major coronary artery with a visually estimated stenosis $\geq 70\%$ reduction in diameter did not receive a bypass graft. *Minimal coronary disease* meant there were no lesions $\geq 70\%$ in a major coronary artery segment and no lesion $\geq 50\%$ in the left main coronary artery. *Surgical priority* was designated as elective, urgent or emergent. *Reoperation* included only repeat operations with coronary artery bypass procedures. The patients were analyzed according to the presence or absence of postoperative angina, with the 1,253 patients having angina at the first postoperative year compared with the remaining 4,036 patients.

Statistical analysis. Baseline characteristics of patients who developed or did not develop postoperative angina were compared using the standard *t* test or chi-square tests for continuous and categorical variables, respectively. A stepwise logistic regression was used to develop a multivariate model in which all variables listed in the univariate table (Table 1) were allowed to enter the model. For recurrent angina in the second and third years, angina status in the previous years was also used as a predictor variable.

Survival probability following the first-year of follow-up was estimated using the Kaplan-Meier method, and the survival difference between patients with angina and those without angina was tested using the log-rank statistic. The Cox regression model was used to estimate the association between recurrent angina and survival adjusted for other factors known to be associated with survival. The rates of reoperation and myocardial infarction at 6 years were estimated by the Kaplan-Meier method and compared by the log-rank test.

Results

Patients. Annual follow-up was obtained in 99.5% of patients. After coronary artery bypass surgery, 24% (1,253 of

Table 1. Univariate Analysis of Characteristics of 1,253 Patients With and 4,036 Patients Without Angina at First Annual Postoperative Follow-Up Visit

	No Angina	Angina	p Value
Age (yr)	54.9 \pm 8.7	53.9 \pm 8.3	< 0.001
Women	16	19	0.03
Current smoker	29	34	< 0.001
Hypertension	35	37	0.13
Diabetes	11	12	0.36
Preoperative angina	92	96	< 0.001
Prior infarction	46	54	0.003
Elective bypass surgery	80	80	0.83
Complete revascularization	74	70	0.003
Vein grafts only	84	88	0.001
Minimal coronary disease	0.75	1.85	0.001

Data presented are mean value \pm SD or percent of patients.

5,289) of patients had angina at the first annual follow-up visit, which increased to >40% by the sixth postoperative year (Fig. 1). *Univariate analysis* (Table 1) showed that patients who had angina in the first postoperative year were younger and more likely to be smokers or to have had preoperative angina or a myocardial infarction. Cessation of cigarette smoking was associated with a reduction in postoperative angina. Postoperative angina was present in the first postoperative year in 27% of current smokers, 23% of former smokers and 21% of those who never smoked ($p < 0.001$). Early appearance of angina was more common with the use of vein grafts only and with incomplete revascularization. This beneficial effect of internal thoracic artery grafts was seen only in the first postoperative year and only in those who had had preoperative angina (93% of patients reported preoperative angina).

Predictors. *Angina* in the first postoperative year was not related to the number of vessels diseased, provided that there was at least one significant lesion in a major coronary vessel. The percent of patients reporting angina was 25% (285 of

Figure 1. Prevalence of angina after coronary artery bypass surgery for the first 6 postoperative years.

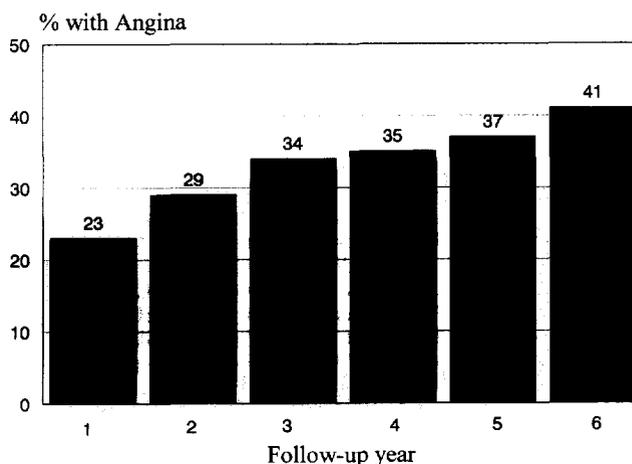


Table 2. Multivariate Analysis of Predictors of Angina During First Postoperative Year

	Relative Risk	p Value
Minimal coronary disease	2.40	0.002
Preoperative angina	2.16	< 0.001
Vein grafts only	1.37	0.002
Prior infarction	1.27	< 0.001
Incomplete revascularization	1.22	0.006
Female gender	1.22	0.02
Current smoker	1.21	0.009
1 yr younger age	1.01	< 0.001

Predictors are listed in order of relative risk estimate.

1,152) for those with single-, 24% (422 of 1,739) for double- and 22% (514 of 2,315) for triple-vessel disease. However, 43% (23 of 53) of patients having no major coronary vessel with $\geq 70\%$ stenosis (i.e., minimal coronary disease) experienced angina in the first postoperative year ($p = 0.04$). Angina in the first postoperative year was not influenced by gender, presence of hypertension or diabetes, surgical priority or ventricular function.

Multivariate analysis (Table 2) showed that the significant predictors of angina in the first postoperative year were minimal coronary disease, preoperative angina, use of vein grafts only, previous myocardial infarction, incomplete revascularization, female gender, smoking and younger age. Predictors of angina in the second postoperative year (Table 3) included, most importantly, angina in the first postoperative year and also female gender, diabetes, hypertension and younger age. Analysis of activity level did not suggest that older patients had less angina than younger patients because of less activity. By the third and subsequent postoperative years (Table 3), the presence of angina can nearly all be explained by

Table 3. Multivariate Analysis of Predictors of Angina During Second and Third Postoperative Years

	Relative Risk	p Value
2nd yr		
Angina in 1st yr	5.88	< 0.001
Female gender	1.56	< 0.001
Preoperative angina	1.46	0.02
Diabetes	1.27	0.01
Hypertension	1.18	0.02
Prior infarction	1.16	0.04
1 yr younger age	1.01	0.003
3rd yr		
Angina in 2nd yr	11.26	< 0.001
Angina in 1st yr	2.70	< 0.001
Preoperative angina	1.82	< 0.001
Incomplete revascularization	1.42	< 0.001
Female gender	1.39	< 0.001
Less than two-vessel disease	1.30	0.003

Predictors are listed in order of relative risk estimates.

Table 4. Multivariate Analysis of Predictors of Mortality in Patients After Coronary Artery Bypass Surgery

	Relative Risk	p Value
Current smoker	1.62	< 0.001
Not elective bypass surgery	1.50	< 0.001
Diabetes	1.48	0.001
Vein grafts only	1.47	0.011
Hypertension	1.42	< 0.001
Incomplete revascularization	1.25	0.019
More vessels diseased	1.22	0.002
Higher left ventricular score	1.14	< 0.001
1 yr older age	1.04	< 0.001
Angina at baseline	0.98	0.93
Angina at 1st follow-up	0.92	0.44

Predictors are listed in order of relative risk estimate.

the status of angina in previous years. Female gender and incomplete revascularization remain significant predictors.

Survival. The presence of angina in the first postoperative year did not affect survival (Fig. 2), with cumulative survival rates at the sixth postoperative year of 88% both for patients with and without angina during their first postoperative year. Multivariate analysis (Table 4) with a Cox regression model using as covariates those variables already shown to be associated with survival for this study group (4) demonstrated that angina in the first postoperative year was not a predictor of mortality. There was no survival benefit for those with angina in the first postoperative year but with relief of angina in the second year compared with those with continuing angina. Angina with onset in the second postoperative year similarly did not affect survival. In patients stratified by the presence or absence of baseline angina, there was no adverse influence on survival from the development of angina in the first postoperative year.

Myocardial infarction (Table 5) during the follow-up period was infrequent, but the probability of infarction occurring was higher in patients with than without angina in the first postoperative year ($p = 0.04$). In addition, the rate of reoperation was higher in patients with than without angina in their first postoperative year ($p = 0.003$).

Discussion

Angina. The incidence of angina after bypass surgery varies considerably among reported studies (2-6), undoubtedly as a result of varying definitions of this clinical entity. In the present study, angina was reported as present even if just one episode occurred per year. Thus, the incidence might be higher than in other studies because of different definitions. Alternatively, the actual incidence may be underestimated because patients who died before their scheduled follow-up visit had unknown postoperative anginal status and could not be included. Appearance of angina in the first postoperative year could be attributed to incomplete revascularization or technical factors leading to perioperative or early graft failure. Progression of disease or vein graft

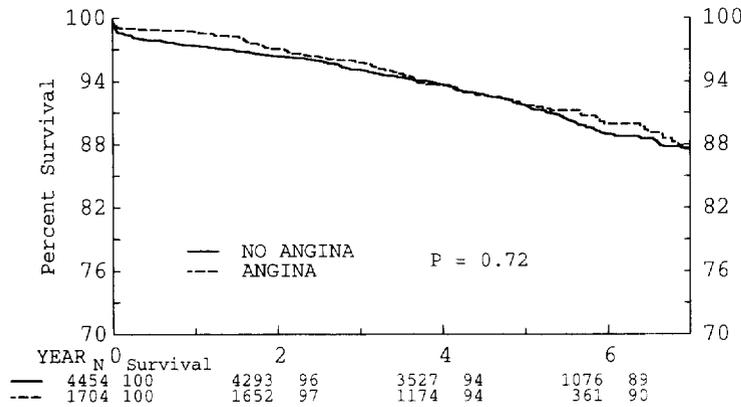


Figure 2. Cumulative survival rates of patients with and without angina in their first postoperative year. **Numbers below abscissa** are number of patients followed up in each group and their survival rates.

failure from accelerated atherosclerosis would not generally be expected to play a role so early postoperatively.

Smoking. The present study demonstrates the value of stopping smoking, even for patients with advanced coronary atherosclerosis requiring coronary artery bypass surgery. In a study (7) of 551 patients with unstable angina or myocardial infarction with a follow-up period of up to 18 years, cessation of smoking was associated with lower overall mortality, although there was no change in the rate of sudden death. Analysis of data from the Multifactor Primary Prevention Trial (8), a study of men with uncomplicated angina pectoris, showed that continued smoking was associated with a less favorable prognosis than that seen in former smokers with angina. These three studies have demonstrated the adverse influence of continued smoking in three different populations. Prompt cessation of cigarette smoking should be a primary goal for all these patients.

Gender. Women were more apt to have angina in the second and subsequent postoperative years. Female gender has been identified as an independent predictor of mortality (9) after coronary artery bypass surgery as well as associated with higher operative mortality rates (10). The postulated reasons for this impaired prognosis include the small body size (11) and thus smaller vessels as well as the more frequent risk factors (12,13), such as diabetes, hypertension and older age, in the women at the time of presentation for coronary artery bypass surgery. In addition, it has been shown that women have lower vein graft patency rates (1). Presumably any of these features could be responsible for the more frequent recurrence of angina in women than in men noted in the present study.

Internal thoracic artery. The internal thoracic artery bypass graft had a beneficial influence on the appearance of early postoperative angina, but this influence did not extend past the

first postoperative year, perhaps because of progression of disease or failure of associated vein grafts. Others have noted both an early (9) and a sustained (14) benefit, with reduction in angina, with the use of the internal thoracic artery for bypass surgery. In addition, these reports noted an improved survival (9) and less need for reoperation (15) in patients with angina and an internal thoracic artery bypass compared with patients with angina and use of vein grafts alone.

Survival. In the present study, angina in the first or second postoperative year did not have a demonstrable adverse effect on survival during the 7-year follow-up period. Early deaths were not included because patients had to be alive at their next follow-up visit to ascertain anginal status and thus to enter the study. As a result, the patients with the worst prognosis, that is, those who died before their first follow-up visit, were excluded, and this exclusion possibly biased the results. It is not known whether this bias equally underestimated mortality in both the angina and no-angina groups. The low overall mortality rate, ~2%/year, and the short follow-up period of 7 years means that there is very little margin to permit the absence of angina to express itself as an improved survival. In studies of patients who do not undergo bypass surgery (8), angina does exert an adverse effect. One study (16) with 54 postoperative patients concluded that over a 1-year follow-up period, patients with unstable angina and previous coronary artery bypass surgery had more fatal and nonfatal cardiac events than those with unstable angina and no bypass surgery. In the current study, which principally included patients with stable angina, recurrent angina was a marker for late myocardial infarction and need for reoperation. However, these events did not adversely affect survival. It is unclear what influence, if any, current practices of angioplasty and other coronary interventions would have on survival. However, there is no reason that the predictors of postoperative angina would be any different under today's standard of care than during the time of CASS enrollment.

Conclusions. The results of the present study show that predictors of postoperative angina are either features that are known before bypass surgery (i.e., preoperative angina, previous myocardial infarction, younger age, female gender, hypertension and diabetes) or are features that might be anticipated

Table 5. Myocardial Infarction and Reoperation for Coronary Artery Disease Over a 6-Year Period in Patients With and Without Angina During First Postoperative Year

	Angina (n = 1,704)	No Angina (n = 4,454)	p Value
Myocardial infarction (%)	0.7	0.5	0.04
Reoperation (%)	3.9	2.1	0.003

before bypass surgery (e.g., incomplete revascularization or use of vein grafts only). Thus, patients with these specific features could be advised before bypass surgery that they would be more likely to experience postoperative angina than those without these features. Cessation of smoking should be emphasized because its benefit is apparent even in the postoperative patient. Finally, the adverse clinical implications of postoperative angina, namely, increased risk of myocardial infarction and need for reoperation, mandate further clinical evaluation of patients with postoperative angina.

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