

# Increased Rehospitalization Rate After Coronary Bypass Operation for Acute Coronary Syndrome: A Prospective Study in 200 Patients

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**Background.** Patients with acute coronary syndrome (ACS) run increased risk of cardiac death or myocardial infarction after coronary artery bypass grafting (CABG). Long-term survival is similar in ACS patients and patients with stable angina pectoris. This study analyzed the cardiac rehospitalization rate up to 10 years after CABG for ACS and stable angina.

**Methods.** CABG was done in 200 patients, 100 with ACS and 100 with stable angina. Troponin-T levels were assayed and the severity of the unstable symptoms was classified according to Braunwald. Early outcome, long-term survival, and freedom from cardiac rehospitalization were analyzed.

**Results.** Three ACS patients died early and 12 died late. In the control group, there were no early and 19 late deaths. The cumulative long-term survival was 85% for the ACS patients and 81% for the stable patients ( $p =$

0.75). Postoperative myocardial infarction occurred in 5 unstable patients and 1 stable patient ( $p = 0.01$ ). At 3 years after the operation, freedom from cardiac rehospitalization was significantly higher in the stable patients (9 vs 27,  $p = 0.001$ ). In the end of the follow-up, there were no differences in the rehospitalization rate.

**Conclusions.** Similar and excellent long-term survival was found in both ACS and stable patients long-term after CABG. In patients with ACS, variables such as elevated troponin-T and angina at rest herald an increased risk of perioperative myocardial infarction. Freedom from cardiac rehospitalization is significantly higher in stable patients compared with ACS patients during the first postoperative years, indicating recurrent ischemia.

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Early surgical revascularization in patients with acute coronary syndrome (ACS) and multivessel coronary disease is currently a well-adopted treatment. There is proven benefit of reduced mortality rates with an aggressive revascularization strategy [1, 2]. Coronary artery bypass surgery grafting (CABG) for ACS has been shown to be an effective and safe treatment with excellent early results [3]. However, the risk of postoperative myocardial infarction (MI) is higher in unstable patients compared with those undergoing an elective operation for stable angina pectoris [4, 5].

Comparisons are difficult in patients with ACS because of their heterogeneous clinical presentation; for example, ACS patients whose symptoms were stabilized on medical treatment had no higher risk of MI compared with stable patients [6]. Cardiac enzyme markers and clinical criteria are both established tools to predict operative risk [7]. Elevated troponin-T levels and ST-segment depression on electrocardiogram (ECG) in ACS correlate with an increased risk of cardiac death and acute MI [8–12]. The severity of angina symptoms is also a risk predictor, where the Braunwald classification is one of the most validated [13].

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Any difference in nonfatal cardiac outcomes late after operations for ACS and stable angina pectoris has been poorly investigated. This prospective study evaluated long-term survival and the late cardiac rehospitalization rate after CABG for ACS and stable angina pectoris.

## Material and Methods

The local Ethics Committee approved the study, and informed consent was obtained from all patients who participated.

### Patients

The study included 100 patients operated on urgently due to ACS and a control group of 100 patients undergoing elective CABG from August 1997 through August 1998. All patients alive were contacted during follow-up. Patients with ACS were treated at the coronary care unit of this or a local hospital until the day of the operation. The ACS patients received standard antianginal and antithrombotic medication. No patient received platelet adenosine diphosphate (ADP) receptor antagonists (eg, ticlopidine or clopidogrel), because these drugs were not established standard treatment for ACS a decade ago.

Patients underwent subacute coronary angiography and were then referred for urgent CABG if the coronary

obstructions were considered unsuitable for percutaneous coronary intervention (PCI). The control group was randomly selected among patients who underwent elective operations on the same day as the ACS patients. Clinical characteristics were similar in the two groups,

Table 1. Clinical Characteristics in Unstable and Stable Patients Undergoing Isolated Coronary Artery Bypass Grafting

Characteristic Median (Range) or No.	ACS (n = 100)	Stable Angina (n = 100)	p Value
Age, y	65 (39–84)	67 (42–82)	0.10
Female gender	19	17	0.71
Smoker			
Current	16	11	0.30
Previous	35	41	0.38
Diabetes mellitus	18	14	0.44
Diet management	2	3	0.42
Oral medication	9	4	0.22
Insulin treatment	7	7	0.53
Hypertension	39	39	>0.99
Hyperlipidemia	46	46	>0.99
Previous thromboembolic event	12	12	>0.99
Reduced LV function (EF < 0.30)	7	6	0.78
Obstructive pulmonary disease	11	8	0.47
Intermittent claudication	4	6	0.52
Previous myocardial infarction	60	46	0.05
1	38	38	0.03
2	16	6	0.09
≥3	6	2	0.27
Previous coronary revascularization	17	5	0.01
Angioplasty	13	5	0.23
CABG	4	0	0.25
Diseased vessels, No.			
1	3	2	0.65
2	19	19	>0.99
3	78	79	0.86
Left main stem stenosis	26	21	0.40
Braunwald class			
IIB	...	38	...
IIC	...	18	...
IIIB	...	28	...
IIIC	...	16	...
Cardiopulmonary bypass, min	80 (26–240)	84 (18–190)	0.36
Aortic cross-clamp (min)	40 (8–98)	43 (8–140)	0.19
Anastomoses/patient	3.4 (1–6)	3.5 (1–6)	0.34

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; EF = ejection fraction; LV = left ventricular.

Table 2. Cause of Early and Late Death in Patients Undergoing Coronary Bypass Grafting for Acute Coronary Syndrome and Stable Angina Pectoris

Cause of death, No. (%)	ACS (n = 100)	Stable Angina Pectoris (n = 100)
Acute myocardial infarction	8 (53)	6 (32)
Cerebrovascular lesion	2 (13)	1 (5)
Malignant disease	3 (20)	7 (37)
COPD	1 (7)	2 (10)
Other	1 (7)	3 (16)
Total	15 (100)	19 (100)

ACS = acute coronary syndrome; COPD = chronic obstructive pulmonary disease.

except for a higher frequency of previous history of MI and revascularization in the ACS group (Table 1).

### Surgical Protocol

The patients were operated on through a median sternotomy using cardiopulmonary bypass at moderate hypothermia at 32 to 34°C. Cold crystalloid modified St. Thomas cardioplegia was used for myocardial protection in 10 unstable and 33 stable patients. The remaining patients received cold oxygenated blood cardioplegia. The cardioplegic solution was cooled to 4°C and given at an initial dose of at least 10 mL/kg. Half this dose was repeated every 10 to 15 minutes. In 57 patients (29%), cardioplegia was given antegrade through a cannula in the aortic root, whereas in 143 patients (71%), it was administered into the coronary sinus at a pressure of 50 mm Hg.

The distal coronary anastomoses were constructed first, and the proximal vein anastomoses to the aorta were sutured while the patient was rewarmed. The median cardiopulmonary bypass and aortic cross-clamp times and the number of coronary artery anastomoses did not differ between the groups (Table 1). An internal mammary artery graft was anastomosed to the left anterior descending artery in 97 of the unstable patients and in 98 of the stable patients ( $p = 0.63$ ).

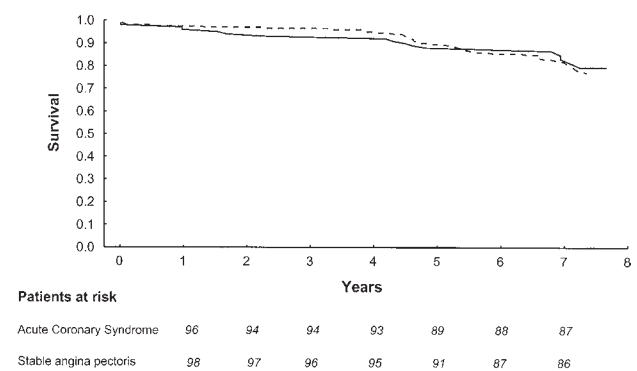


Fig 1. Cumulative survival after coronary artery bypass grafting for acute coronary syndrome (solid line) and stable angina pectoris (dashed line).

**Definitions and Statistical Methods**

A troponin-T level higher than 0.1 µg/L was considered elevated and an indication of minor myocardial cell damage. Postoperative heart failure was defined as the need for pharmacologic inotropic support or intra-aortic balloon treatment. A perioperative MI was defined by the criteria used in 1997 to 1998: the appearance of new Q wave or disappearance of R wave in 2 or more adjacent leads on a postoperative ECG tracing, or one or more of creatine kinase exceeding 20 microkat/L and aspartate aminotransferase exceeding 3 microkat/L, with an aspartate aminotransferase/alanine aminotransferase ratio exceeding 2 within the first 48 hours postoperatively indicated an perioperative MI.

Time and cause of death were obtained from the Swedish National Cause of Death Register. Data on hospitalizations during the follow-up period was obtained from a continuously updated national register on all hospital admissions in Sweden. The Mann-Whitney's *U* test was used to compare two distributions. Discrete variables were analyzed with  $\chi^2$  analyses. Cumulative long-term survival and postoperative hospitalization rates were analyzed using the Kaplan-Meier method. A value of  $p < 0.05$  was considered statistically significant.

**Results**

**Early Deaths and MI**

Three of the ACS patients died within 30 days of the operation of stroke, low cardiac output syndrome, and deep sternal wound infection, respectively. None of these patients fulfilled the ECG or enzymatic criteria for postoperative MI and none had an elevated troponin-T level before the operation. A perioperative MI occurred in 5 unstable patients and 1 stable patient ( $p = 0.01$ ).

**Late Death**

The mean follow-up was 6.5 years (range, 0.1 to 7.7 years). A total of 12 late deaths occurred among patients with ACS and in 19 controls ( $p = 0.75$ ). The causes of death are

listed in Table 2. Overall survival was 85% for patients with ACS and 81% for stable patients. Freedom from cardiac death was 92% in the unstable patients and 94% in the stable patients. The most common cause of death was acute MI in unstable patients and malignant disease in stable patients (Table 2). During the first 4 years of follow-up, there was a tendency of increased death among the ACS patients, but it did not reach statistical significance (Fig 1).

**Readmission for ACS**

A significantly higher proportion of the ACS patients (27 vs 9,  $p = 0.001$ ) were rehospitalized because of angina pectoris or acute MI during the first 3 years postoperatively (Fig 2). The long-term survival, however, was similar in the ACS and stable patients. The increased cardiac rehospitalization rate in the ACS group reflects a higher proportion of ischemic events in ACS patients compared with patients with stable angina pectoris. By the end of the follow-up period, stable patients were also hospitalized to a greater extent, thus reducing the differences between the groups (Fig 2).

**Comment**

New effective antithrombotic therapies, advanced ECG tracings with continuous ST analysis, and early revascularization are among current practice to protect patients from acute MI [10, 12, 14]. All patients with ACS receive high doses of platelet ADP-receptor antagonists (eg, clopidogrel), in addition to the traditional acetylsalicylic acid treatment, to reduce the risk recurrent ischemia and cardiac death [15]. This was not the case a decade ago (1997 to 1998), when the patients in this study were included. The beneficial effect of dual antiplatelet treatment in ACS is indisputable, even though a higher incidence of major bleeding has been reported [16]. Clopidogrel resistance has been observed in several patients, and its clinical effect on prognosis is under continuous evaluation [17, 18]. Reports have focused on the presence of residual platelet activity after CABG, and research has demonstrated that high residual platelet reactivity is independently correlated to a worse clinical outcome in patients treated with CABG [19, 20].

Today it is well established that ACS is caused by plaque rupture and intracoronary thrombus formation; hence, stable and ACS patients differ, not only in clinical presentation, but also in the underlying pathophysiologic mechanism. It is reasonable to assume that patients with ACS still have an increased risk of new acute cardiac events, even after surgical revascularization. An optimal antiplatelet medication is therefore of great importance.

The present study was conducted to address the question if ACS, previously shown to be associated with an increased perioperative risk, affects the long-term outcome after CABG. The results strongly support there being different prognoses between the patient groups, because patients operated on due to ACS had a significantly higher rehospitalization rate compared with patients with stable angina during the first years of follow-

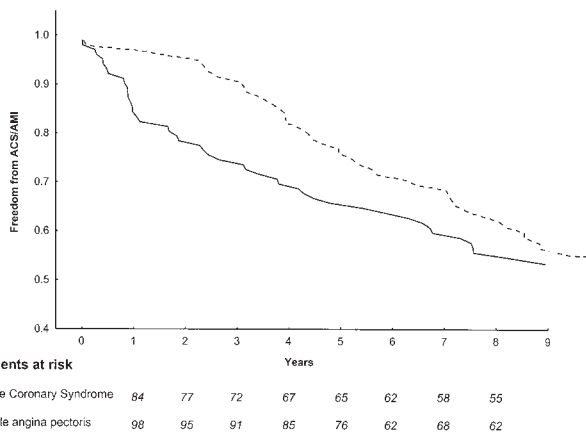


Fig 2. Freedom from rehospitalization for acute coronary syndrome/acute myocardial infarction (solid line) and stable angina (dashed line) after coronary artery bypass grafting.

up. In the long-term, the difference was reduced, and in the end of the follow-up period, the cumulative rate of rehospitalizations was similar (Fig 2).

I do not believe that any revascularization method can change the plaque vulnerability in the coronary arteries. The bypass grafts, attached distally on the coronary vessels, protect the patients from fatal coronary occlusions, supported by the finding of similar long-term survival in the two patient groups. However, the ACS patients still had an increased coronary event rate and needed hospitalization more often. It is reasonable to assume that differences in plaque vulnerability, with a persistently higher rate of intracoronary thrombus formations, also resulted in more angina episodes in the ACS patients.

The current standard antithrombotic treatment in ACS and stable patients after CABG is acetylsalicylic acid (75 to 320 mg). Patients treated with percutaneous coronary intervention (PCI), however, receive dual antiplatelet therapy (eg, acetylsalicylic acid and clopidogrel) for 6 to 12 months, depending on the type of stent that was inserted.

Little is known on any beneficial effects of introducing dual antiplatelet therapy after CABG. In a substudy of the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, clopidogrel therapy was independently associated with a 31% relative risk reduction in vascular death, MI, stroke, or rehospitalization in patients with a history of cardiac operations [21]. A major pitfall in the CAPRIE study is the lack of information about the type of cardiac procedure. Thus, it is likely that patients operated on for other diseases than coronary artery disease were included in the analysis [21, 22].

In the Clopidogrel in Unstable angina to Prevent Recurrent Ischemic Events (CURE) trial, 2072 of 12,562 patients (16.5%) underwent CABG. The patients randomized to clopidogrel treatment had a slightly more favorable outcome vs the control patients, mainly before the CABG procedure, where 71 in the treatment group (6.7%) experienced the primary end point compared with 57 in the control group (5.6%). After the operation, however, there was a similar event rate in the placebo and clopidogrel groups [23]. In a small, randomized study, clopidogrel failed to inhibit platelet function early after CABG [17, 18].

No solid, randomized data currently support any beneficial effect of continuing clopidogrel treatment after CABG. The present study demonstrates differences in long-term outcome in patients with ACS and stable angina after CABG, illustrated by differences in the cardiac rehospitalization rate. To what extent a more intense postoperative antiplatelet medication has clinically beneficial effects after CABG has to be further evaluated. Such an analysis must account for presence of clopidogrel resistance, the risk of severe bleeding complications, and the increased medical cost.

The study has several limitations. The nonrandomized study design always has a risk of selection bias; however, the random selection of the control group as well as similar baseline characteristics speaks against major dif-

ferences in the study groups. Another limitation is the risk of a type II error due to a small study groups in the mortality analysis. The fact that 165 patients were still alive at the end of the long observation time of 6.5 years indicates reasonable reliability in the data analysis. The study was sufficiently powered to discover clinical relevant differences in rehospitalization pattern in the two study groups.

In summary, patients with ACS underwent urgent CABG with an increased perioperative risk. CABG offers excellent and similar long-term survival for patients with ACS and those with stable angina pectoris. The ACS patients had a significantly higher rate of cardiac rehospitalization the first years after surgical revascularization, indicating recurrent ischemia. A more effective antiplatelet medication after CABG can possibly reduce the risk of late recurrent intracoronary thrombotic events in patients with ACS. Before any definite change in the postoperative antiplatelet practice, the hypothesis must be confirmed in further trials.

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