

# Mediastinitis After Coronary Artery Bypass Grafting Risk Factors and Long-Term Survival

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**Background.** Mediastinitis is a severe complication of coronary artery bypass grafting. The aim of the present study was to determine incidence of mediastinitis, its risk factors, and its effect on early and long-term survival.

**Methods.** The study has a dual design, a case-control, and a retrospective cohort, using a source population of 18,532 consecutive patients who underwent coronary artery bypass grafting from January 1989 to December 2000. The closing date was February 1, 2008. Median follow-up was 10.3 (range 8.1 to 18.9) years. Patients with mediastinitis were compared with a random control group without mediastinitis issued from the same source population in a ratio 1:4. The crude effect of mediastinitis was estimated using rate ratio and 95% confidence limits. Adjustment for multiconfounders was done with the Cox model. A logistic model was used to pinpoint risk factors of mediastinitis. Calibration and discrimination of a prognostic model was done.

**Results.** One hundred seven patients (0.6%) developed mediastinitis. Diagnosis was made 12 (9 to 19) days postoperatively. Independent risk factors of mediastinitis using the logistic model were advanced age, male gender, left main stenosis, body mass index  $30 \text{ kg/m}^2$  or greater, chronic obstructive pulmonary disease, diabetes, and increased amount of blood transfusion. There was no

increased risk of early mortality (odds ratio = 0.58; 95% confidence interval 0.13 to 2.61) ( $p = 0.48$ ) but there was increased risk of morbidity (intraaortic balloon pump, ventricular and supraventricular arrhythmia, stroke, inotropes, and myocardial infarction). Follow-up had a median observation time of 10.3 years. Survival for patients with mediastinitis was  $49.5 \pm 5.0\%$  versus  $71.0 \pm 2.2\%$  for controls ( $p < 0.01$ ). Analysis of specific death causes documented that cardiac deaths were significantly more frequent in mediastinitis patients than in control patients. When controlling for the confounding effect of the other variables (age, cardiopulmonary bypass time, body mass index, chronic obstructive pulmonary disease), the hazard ratio associated with mediastinitis on long-term mortality was 1.59, 95% confidence limits (1.16 and 2.70) ( $p = 0.003$ ).

**Conclusions.** The incidence of mediastinitis in 18,532 patients undergoing coronary artery bypass grafting surgery was low. The major preventable risk factor of mediastinitis was amount of blood transfusion. Mediastinitis had an excess risk of early morbidity and was associated with a significant reduced long-term survival. Most deaths were considered to be cardiac.

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The reported incidence of mediastinitis after coronary artery bypass grafting (CABG) is 0.4 to 4%. Mediastinitis is associated with increased morbidity, mortality, and cost [1–10].

The traditional management consists of reoperation with debridement and drainage, followed by prolonged hospitalization for antibiotic therapy. Early or in-hospital mortality is reported to vary between 10 and 47% [1–7].

The etiology and pathophysiology of mediastinitis is complex and multifactorial. Previous studies have listed a number of factors associated with mediastinitis [1–10]. In the present study a case-control design was undertaken in order to evaluate preoperative, intraoperative, and postoperative risk factors of mediastinitis for patients undergoing sole CABG. As the long-term effect of medi-

astinitis on mortality after CABG has not been thoroughly well studied, a retrospective cohort analysis was performed to study the early and late effects of mediastinitis concerning survival.

## Material and Methods

### Source Population

The study was approved by the Regional Medical Ethics Committee and represents a multicenter collaboration between Rikshospitalet University Hospital, The Feiring Heart Clinic, and Oslo Heart Center. The institutions maintain the same diagnostic criteria and treatment with active and prospective epidemiologic surveillance of hospital infections. Between January 1989 and December 2000, a total of 18,532 adult patients undergoing CABG surgery were considered in our analysis. The diagnosis of poststernotomy mediastinitis was based upon the criteria established by the Centers for Disease Control and Prevention [11, 12].

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### Study Design

This study has a double design, where the first one is a case-control. Cases are patients who developed mediastinitis, and controls are patients without mediastinitis, coming from the same source population. The other is a cohort with long-term follow-up, and endpoints total mortality. In the source population mediastinitis occurred in 107 patients during the first postoperative weeks. A random sample of 444 patients was extracted from patients not suffering from mediastinitis and from the same source population. This was used as a control for the cases in a case-control design (Fig 1).

Another design was a cohort of exposed (mediastinitis) and nonexposed (nonmediastinitis) with outcome, early mortality and morbidity, and long-term survival (median follow-up 10.3 years). The nonexposed represent the control group. For each incident case of mediastinitis, four random controls without mediastinitis were considered. Matching was not performed as it does not control for confounding in the case-control design, and could introduce unknown confounders as advised by Kleinbaum and colleagues [13] and Rothmann and colleagues [14].

### Statistical Methods

For the case-control study, after univariate analysis the multivariate analyses were used to pinpoint independent risk factors of mediastinitis. Association between risk factors and mediastinitis were estimated by the odds ratio (OR) and 95% confidence interval (CI).

Independent risk factors were pinpointed by a backward elimination procedure, using a multivariate logistic model [13]. As we are in a prognostic strategy in the case-control analysis the predictive accuracy of the model were evaluated by calibration and discrimination.

Calibration, which measures the ability of the model to assign the appropriate risk, was evaluated by the Hosmer and Lemeshow (H-L) goodness of fit test. The H-L  $\chi^2$  measures the difference between expected and observed outcomes over deciles of risk.

A statistically not significant H-L result ( $p$  value > 0.05) suggests that the model predicts accurately on average. Discrimination, which measures the ability of the model to differentiate among those who have or have not suffered mediastinitis, was evaluated by the analysis of the area under the receiver operating characteristic curve. If the area under the curve is greater than 0.7 it can be concluded that the model has an acceptable discriminatory capability.

For the cohort study the association between presence (yes/no) of mediastinitis and early mortality and morbidity was quantified using odds ratio and its 95% confidence limit (CL). In this study our strategy was explanatory, describing the crude effect of mediastinitis on long-term survival, and the adjusted effect when controlling for major confounders [15]. This is a dynamic cohort where date of surgery is time of entry in the cohort, and mortality is the major outcome. It is censored survival data where the response is mortality, and patients not dying were censored at the closing date of the study which was February 1, 2008. Long-term survival was estimated univariately by survival curves using the Kaplan-Meier method and comparison of the survival curves was done by the Breslow and Mantel-Cox test [16, 17]. A stratification analysis using the Mantel-Haenszel methods adapted to person/years was done to quantify confounders and pinpoint effect modifier using the Breslow-Day test of heterogeneity [13]. Crude effect of mediastinitis on total mortality using the patient/years model was estimated. The adjusted effect of mediastinitis on long-term survival, controlling for multiconfounders, was done using the Cox model [17].

It is standard practice in epidemiologic research studies to compare observed survival in a cohort versus the expected survival in a reference population (the national population) of the same age and sex distribution. The method of standard mortality ratio (SMR) analysis consists of applying age and gender specific rates of death of the total Norwegian population to the cohort of heart-operated patients to yield a number of expected deaths. The SMR is the ratio of total observed deaths in the cohort divided with the total of expected deaths in the same population. The 95% confidence limit is estimated by the method of Rothman and colleagues [14]. In most instances the SMR should be regarded with caution when the expected value is less than 2. Such results could be misleading except when the disease is rare in the nonexposed population.

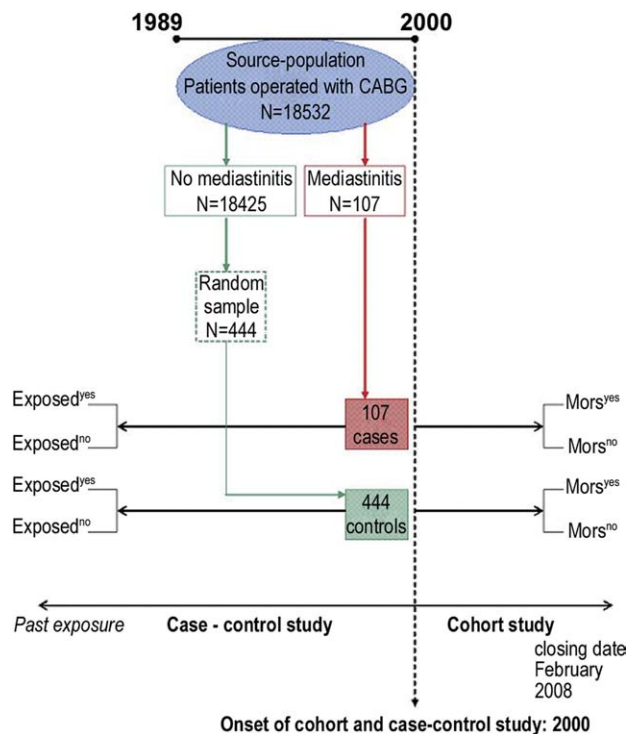


Fig 1. Study design of cohort and case-control study. (CABG = coronary artery bypass grafting.)

*Power Analysis: Case-Control Design*

A prestudy power analysis was done using estimates from the literature [1, 2, 7]. One of the hypotheses

concerned obesity, defined as body mass index (BMI) 30 kg/m<sup>2</sup> or greater. The frequency of obesity was 3% in patients without mediastinitis. Patients with mediastini-

Table 1. Univariate Risk Factors of Mediastinitis

Characteristics	Mediastinitis (n = 107)	Controls (n = 444)	p Value
<b>Preoperative:</b>			
Age (years)	65.0 (±9.3)	62.4 (±9.6)	<0.01
<b>Gender:</b>			
Male (%)	94.4	75.7	<0.01
Female (%)	5.6	24.3	
<b>Vessels involved (n)</b>			
I	1	4	0.99
II	9	42	
III	56	320	
Left main stenosis (n)	24/107	64/444	0.04
Emergency surgery (n)	17/107	78/444	0.57
Unstable angina (n)	26/107	83/444	0.19
Body mass index (kg/m <sup>2</sup> )	27.3 (±4.2)	26.0 (±3.6)	0.01
Preopr. S-hemoglobin (g/dL)	13.7 (±1.9) (n = 99)	13.8 (±1.8) (n = 389)	0.39
Preopr. S-creatinine (μmol/L)	117 (±69) (n = 95)	105 (±56.6) (n = 353)	<0.01
Uremia (n) S-creatinine > 200 μmol/L	5/107	10/444	0.17
Hypercholesterolemia.(n)	26/107	112/444	0.94
Hypertension (n)	37/107	110/444	0.05
Smoking history (n)	53/107	213/444	0.77
Previous cardiac surgery (n)	4/107	24/444	0.48
<b>Previous myocardial infarction (n)</b>			
Previous cerebral stroke (n)	5/107	8/444	0.08
Preopr. atrial fibrillation (n)	8/107	22/444	0.30
Chronic obstructive pulmonary disease (n)	19/107	31/444	<0.01
Diabetes (n)	26/107	45/444	<0.01
<b>Functional NYHA-classification (I-IV)</b>			
I-II	23/107	112/444	0.53
III-IV	84/107	334/444	
General atherosclerosis (n)	18/107	37/444	<0.01
Left ventricular ejection fraction; EF ≤ 0.40	13/107	32/444	0.09
<b>Operative:</b>			
Left internal mammary artery (n)	98/107	397/444	0.50
Right internal mammary artery (n)	1/107	3/444	0.78
Number of distal anastomoses	3.6 (±1.0)	3.5 (±1.1)	0.76
Aortic cross-clamp time (minutes)	38.8 (±15.3)	36.3 (±14.7)	0.13
Cardiopulmonary bypass time (minutes)	73.1 (±26.5)	68.1 (±27.1)	0.04
<b>Postoperative:</b>			
Mediastinal drainage (mL)	759 (±431)	784 (±545)	0.79
Retransfusion (mL)	580 (±334)	600 (±403)	0.99
Ventilation time (hours)	6.0 (±15.0)	7.0 (13.0)	0.18
Reoperation for bleeding (n)	12/107	21/444	0.01
Blood transfusion (units)	4.0 (±7.3)	1.6 (±4.6)	<0.01
Postopr. ventricular and supraventricular arrhythmia (n)	40/107	143/444	0.30
Postopr. cerebral stroke (n)	5/107	8/444	0.08
Postopr. myocardial infarction (n)	5/107	9/444	0.11
Intraaortic balloon-pump (n)	8/107	16/444	0.08
Inotropy (n)	10/107	20/107	0.07
Multiorgan failure (n)	3/107	6/444	0.29

NYHA = New York Heart Association; Preopr. = preoperative; Postopr. = postoperative.

Table 2. Independent Risk Factors of the Endpoints of Mediastinitis Using the Multivariate Logistic Mode

Variable	Level	OR	95% CI	p Value
Age > 70 (n)	1/0	1.75	1.05-2.91	0.03
Male gender (n)	1/0	7.90	3.20-19.93	0.0001
Left main stenosis (n)	1/0	1.96	1.08-3.56	0.03
Body mass index ( $\geq 30$ kg/m <sup>2</sup> )	1/0	2.96	1.62-5.96	0.0001
Presence of chronic obstructive lung disease (n)	1/0	2.53	1.28-5.01	0.008
Presence of diabetes (n)	1/0	3.29	1.81-5.96	0.0001
Blood transfusion (units)	>10 units	3.96	1.60-9.60	0.002

CI = confidence interval; OR = odds ratio.

tis had a 3.6 higher risk of being exposed to obesity. This permitted us to estimate a priori power for our study.

Considering four controls per case of mediastinitis and a type I error of 5% and a power of 80%, we would need a minimum of 103 cases of mediastinitis and 412 controls. This sample size would provide high power to pinpoint a large spectrum of independent risk factors [14, 15].

*Power Analysis: Cohort Design*

The power analysis was done at the planning phase of the study. We used the results from the studies of Milano and colleagues [1], where they stipulated a 2-year cumulative mortality in patients without mediastinitis to 10.1% and 23% for patients with mediastinitis. For a relative risk = 2, type I error of 5%, power of 80%, and a ratio of nonexposed to exposed of 4:1 we would need a total of 115 cases with exposed mediastinitis and 460 patients not exposed to mediastinitis.

*Surgical Technique in the Primary Heart Operation*

In all patients the primary operative approach was a median sternotomy, with cardiopulmonary bypass and systemic moderate hypothermia, using antegrade crystalloid cardioplegia. Standard technique included routine use of the left internal mammary artery, with supplemental vein grafts to obtain complete revascularization. Mediastinal

shed blood was retransfused. The patients received standard antibiotic prophylactics with four doses of intravenous cephalotin (2 g) for at least 24 hours or until all drains or monitor lines had been removed.

*Surgical Revision of Mediastinitis*

All patients were treated with debridement, irrigation, and rewiring of the sternum, as described by Robicsek and colleagues [18]. Debridement was followed by continuous irrigation with antibiotic solution until the effluent drainage had been free from bacterial growth. If this technique did not provide healing, plastic surgical reconstruction with a muscle flap was employed.

**Results**

*Risk Factors of Mediastinitis Using the Case-Control Design*

The two groups of patients were comparable with respect to preoperative, intraoperative, and postoperative variables (Table 1). Mediastinitis occurred in 107 (0.6%) of 18,532 patients. The time between surgery and onset of symptoms was 12 (9 to 19) days. Irrigation time was 7 (1 to 24) days.

Independent risk factors of mediastinitis were pinpointed using the logistic model. Our results are summa-

Table 3. Univariate Analysis of Risk Factors of Early (30-Day) Mortality and Morbidity

Mortality/Morbidity	Level	%	OR	95% CL	p Value
Endpoint death:					
Early mortality	Yes	2/107 = 1.4%	0.58	0.13 and 2.61	0.48
	No	14/444 = 3.2%			
Endpoint morbidity:					
Intraaortic balloon pump	Yes	8/107 = 7.5%	2.1	0.90 and 5.20	0.078
	No	16/444 = 3.6%			
Postoperative ventricular or supraventricular arrhythmia	Yes	36/107 = 33.6%	1.86	1.17 and 2.90	0.008
	No	95/444 = 21.4%			
Peroperative stroke	Yes	5/107 = 4.8%	2.6	0.90 and 8.30	0.079
	No	8/444 = 1.8%			
Postoperative inotopia	Yes	13/107 = 12.1%	2.13	1.06 and 4.30	0.030
	No	27/444 = 6.1%			
Postoperative myocardial infarction	Yes	5/107 = 4.7%	2.36	0.77 and 7.20	0.120
	No	9/444 = 2.0%			

OR = odds ratio; CL = confidence limits.

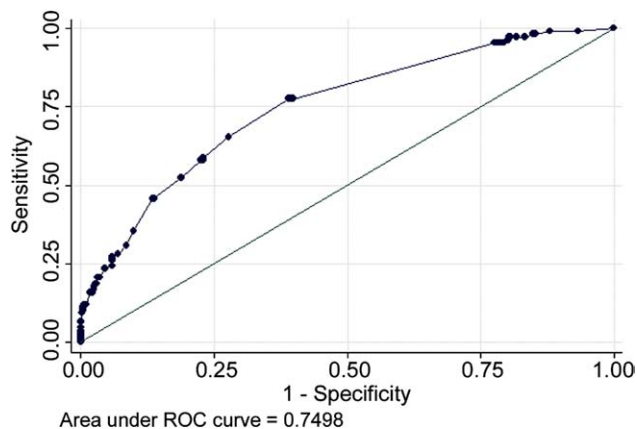


Fig 2. Receiver operating characteristic (ROC) curve for mediastinitis using the logistic model.

rized in Table 2. Age over 70 years had a 74% increased risk compared with younger patients, and male gender had a 7.9 higher risk of developing mediastinitis than female gender.

Presence of left main stenosis (LM) had a 90% increased risk compared with a patent LM, obesity defined as BMI 30 kg/m<sup>2</sup> or greater had a 2.9 increased risk compared with patients having a BMI less than 30 kg/m<sup>2</sup>. Chronic obstructive pulmonary disease (COPD) had a 2.5 increased risk compared with the absence of this condition, and presence of diabetes mellitus had a 3.28 increased risk compared with the absence of this condition. Finally, blood transfusion with an amount of more than 10 packs of blood carried 3.9 increased risks, compared with a less quantity of packs transfused.

As we are in a prognostic strategy the calibration and discrimination of the model are important issues. The calibration has been assessed by plotting the observed proportion of events against the predicted probabilities by groups defined by predicted risks. Goodness of fit was tested with the H-L test ( $\chi^2 = 1.35$ , number of groups 7, *p* value = 0.9871). The H-L test was not significant, indicating a useful goodness of fit. These results indicate that the model predict accurately, both on average and across the ranges of patients, deciles of risk; hence, it is suitable for use in all (low to high-risk patients).

The risk of mediastinitis model developed demonstrates an acceptable discriminatory power as area under the receiver operating characteristic curve was 0.7498, 95% CL (0.711 and 0.785) (Fig 2).

#### Effect of Mediastinitis on 30-Day Mortality and Morbidity Using the Cohort Design

There was no increased risk of early mortality (OR = 0.58; 95% CI 0.13 to 2.61) (*p* = 0.48) (Table 3). Considering early morbidity, there was increased risk of postoperative ventricular- or supraventricular arrhythmia (OR = 1.86, 95% CI 1.17 to 2.90) (*p* = 0.008), and postoperative use of inotropia (OR = 2.13; 95% CI 1.06 to 4.30) (*p* = 0.03), borderline for the use of intraaortic balloon pump (OR = 2.1; 95% CI 0.9 – 5.20) (*p* = 0.08) and perioperative stroke

(OR = 2.6; 95% CI 0.90 to 8.30) (*p* = 0.08), and for perioperative myocardial infarction (OR = 2.36; 95% CI 0.77 to 7.20) (*p* = 0.12). The borderline significance of the last two events was due to power deficiency.

Reconstruction of the sternum was successfully achieved in 92 patients using the Robicsek technique. In 10 patients the wound had to be closed by use of mobilized muscle flaps (mean 25, 2 to 109 weeks) after the primary operation. Furthermore, in three patients chronic sternal fistulas occurred during the follow-up period.

Two patients died within 30 days; one from myocardial infarction on the 17th postoperative day and the other of sepsis and disseminated intravascular coagulation 25 days after the primary CABG operation. According to the National Death Index all the 14 control patients in the early mortality group died of ischemic heart disease.

#### Postoperative Bacterial Findings

At revision for mediastinitis, cultures were taken. Bacterial growth was positive in 85 patients (79.4%). The results of our bacterial tests performed are summarized in Table 4.

#### Effect of Mediastinitis on Long-Term Survival Using the Cohort Design

The 10-year, long-term survival for patients with mediastinitis was 49.5 ± 5.0%, compared with 71.0 ± 2.2% in nonmediastinitis patients; log-rank test (*p* < 0.01) (Fig 3). The rate ratio takes into consideration that the follow-up time was 2.01. The crude effect shows that CABG patients with mediastinitis had a double risk of mortality compared with the controls (Table 5).

On the other hand, Figure 4 shows the instantaneous hazard function (instantaneous force of mortality) during the 19 years of follow-up. This figure pinpoints an increasing risk over time for patients with mediastinitis as compared with the controls without mediastinitis. A stratification analysis, using the Mantel-Haenszel person/years method, showed that age (10-year intervals) had the largest confounding effect of 12.3%, while cardiopulmonary bypass time (20-minute intervals) and BMI had a 9% confounding effect. The presence of COPD had a weaker confounding effect of 6% when adjusting simultaneously for the confounding effect of age, cardiopulmonary bypass time, BMI, and COPD using the Cox model. The hazard ratio was 1.59

Table 4. Microorganisms Associated With Mediastinitis in 107 Patients

Type of Microorganisms	No.	%
<i>Staphylococcus aureus</i>	53	49.5
<i>Staphylococcus epidermidis</i>	20	18.7
<i>E-coli</i>	4	3.7
<i>Enterobacteriae</i>	4	3.7
<i>Pseudomonas aeruginosa</i>	3	2.8
<i>Bacteroider fragilis</i>	1	0.9
No growth	20	18.7
No test performed	2	1.9

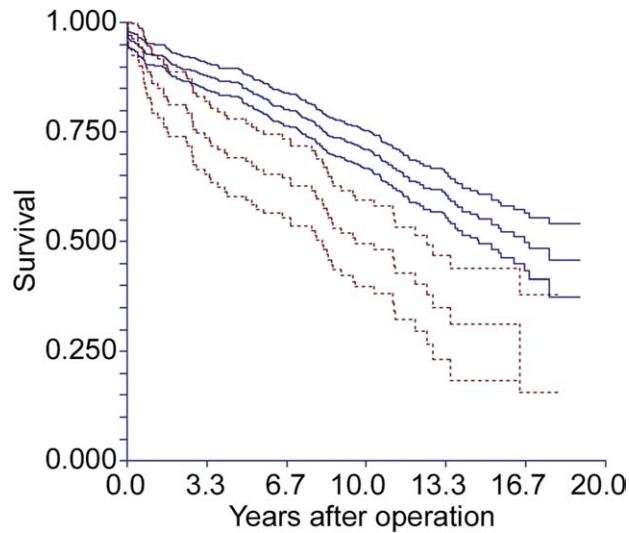


Fig 3. Survival of patients with and without mediastinitis and 95% confidence limits. (.. = yes; — = no.)

with 95% CL (1.16 and 2.17) ( $p = 0.003$ ), indicating a 59% increasing risk of total mortality for patients with mediastinitis as compared with the patients without mediastinitis during all the time of follow-up.

#### Comparison With the Total Norwegian Population

We compared the subcohort of patients with mediastinitis, stratified by gender and age, to the total Norwegian population, matched by age and gender. For the male patients with mediastinitis (101 patients), the estimated SMR was 3.9 with 95% CL (3.03 and 5.04), while for the subcohort for males without mediastinitis the SMR was 2.5. The 95% CL (2.10 and 3.05), indicates a higher risk of mortality for male patients suffering from mediastinitis compared with the male not having this condition. The subcohort of females with mediastinitis included only 6 patients. Expected mortality was less than 2, making it incorrect to calculate SMR.

#### Cause of Mortality

The National Office of Statistics was used to assess specific cause of death for the patient population. Cardiac death was significantly more frequent in the mediastinitis group compared with the nonmediastinitis group. Cardiac death after 10 years for patients with mediastinitis was 34.6% compared with 21.4% in nonmediastinitis patients ( $p < 0.006$ ). In the mediastinitis group cardiac-related deaths were found in 37 (34.6%) patients (ischemic heart disease 35, valvular disease 1 and arrhythmia 1) and noncardiac-related deaths in 19 (17.8%) patients (malignant disease, 8; diabetes mellitus, 5; chronic obstructive pulmonary disease, 3; and others, 3). In the nonmediastinitis group, 95 (21.4%) patients died of cardiac diseases (ischemic heart disease, 91; valvular disease, 2; heart insufficiency, 2) and noncardiac-related deaths in 70 (15.8%) patients (malignant disease, 25; cerebral disease, 13; diabetes mellitus, 7; COPD 4; renal insufficiency, 4; pneu-

Table 5. Quantification of the Confounding Effect of the Association Between Mediastinitis and Total Mortality: Stratification Using Person/Years Model

Crude Effect	RRc	Confounding Effect
Mediastinitis (n = 551)	2.01 (1.49–2.70)	
Adjusted effect on mediastinitis on total mortality using the Person/Years model for one variable		
Variable	RRa	%
Age ( $\Delta$ 10 years) (n = 551)	1.76 (1.31–2.37)	12.4
Body mass index (BMI $\geq$ 30 kg/m <sup>2</sup> ) (n = 551)	2.19 (1.63–2.95)	9.0
Cardiopulmonary bypass time ( $\Delta$ 20 minutes) (n = 551)	1.83 (1.36–2.46)	9.0
Chronic obstructive pulmonary disease (Yes/No)	1.89 (1.39–2.55)	6.0
Simultaneous Control for Multiconfounders <sup>a</sup>		Hazard Rate
Using Cox's model	1.59 (1.16–2.17)	20.2

<sup>a</sup> Age, body mass index, cardiopulmonary bypass time, and chronic obstructive pulmonary disease.

Breslow test of heterogeneity was not significant for all the different potential confounders.

Confounding effect:  $(RRa - RRc / RRc) \times 100$ .

RRa = adjusted rate ratio; RRc = crude rate ratio.

monia, 3; gastrointestinal ischemia, 3; abdominal aortic aneurysm, 3; and others, 8) ( $p = 0.72$ ). Cardiac death was significantly higher for the mediastinitis group compared with the nonmediastinitis ( $p = 0.006$ ).

#### Comment

##### Risk Factors of Mediastinitis

Multivariate analysis identified six preoperative variables as highly significant independent predictors for the

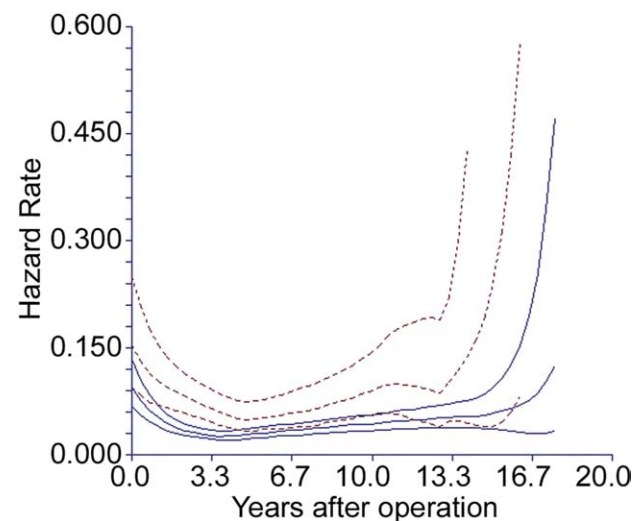


Fig 4. Hazard of mortality for patients with and without mediastinitis and 95% confidence limits. (.. = yes; — = no.)

development of mediastinitis. Four of these risk factors (diabetes, obesity BMI  $\geq 30$  kg/m<sup>2</sup>, COPD, and age) have often been associated with occurrence of mediastinitis [1-10]. In addition we found male gender and LMS to be significantly associated with mediastinitis.

Diabetes mellitus turned out to be one of the most important predictors of mediastinitis. This is in agreement with previous reports [5, 7, 19], although in contrast to others [1-3, 6, 8]. Obesity has been identified as the most important independent predictor of mediastinitis [1, 3, 4, 7]. Our study confirmed the significance of obesity.

We identified COPD disease to be an independent risk factor of mediastinitis in line with other studies [4, 20]. Smoking history was not statistically significant either in univariate or in multivariate analysis, although respiratory distress and pneumonia may occur more frequently in these patients [2, 3, 7]. Age was a significant risk factor for mediastinitis in our study in contrast to some other studies [21, 22]. Cardiopulmonary bypass time was a risk factor in the univariate analysis, but not in the multivariate analysis. The bypass time has been found important in some other reports [1, 3, 20].

There is a link between the length of preoperative hospital stay, and colonization with hospital bacterial flora and inoculation of microorganisms into cutaneous and subcutaneous tissue [23, 24]. We could not detect this association, probably because of very short preoperative hospitalization periods.

The strongest independent risk factor of mediastinitis in our study was male gender. Men had significantly higher rates of diabetes than women. This is in accordance with some other publications [5, 25]. The mechanisms by which men are more predisposed to mediastinitis than women are not known and have to be speculative. Anatomically, women differ from men by having a better collateral flow to the sternum after internal mammary artery harvest [3, 19, 26]. In addition, men have more hair follicles in the area for sternotomy, which may dispose for bacterial growth and infection.

Left main stenosis turned out to be an independent risk factor. This finding is new, and difficult to explain. The amount of blood transfusion (over 10 units) was the only independent postoperative risk factor. This may be explained by a decrease in immune function after homologous blood transfusion [3, 23, 27].

Our results underline the need for preventive measures. Measures include weight reduction (in case of elective surgery), weight adapted perioperative antibiotic treatment, and a strict antidiabetic regimen.

#### *Mediastinitis and Early Morbidity and Long-Term Survival*

In the present study mediastinitis after CABG surgery was associated with a marked increase in morbidity and long-term mortality rates. Strategies for reduction of mediastinitis included the use of an antimicrobial prophylaxis standard aseptic surgical technique, attention to hemostasis, and precise sternal closure, as also underlined in previous reports [1-10].

Hospital mortality of mediastinitis is frequently related to uncontrolled infection, sepsis, and multiorgan failure. Early diagnosis of mediastinitis may improve short-term results, in particular by preventing development of these devastating complications. We report that mediastinitis did not increase early mortality. This could be due to power deficiency as far this endpoint in our study.

The observed effect of mediastinitis on true long-term survival is novel information. Post-CABG mediastinitis is associated with a substantial lower survival compared with patients without mediastinitis.

This study has a median follow-up of 10.3 years, and a range of less than one year to a maximum of 18.9 years. This was the longest follow-up time compared with other studies. Milano and colleagues [1] had a median follow-up of two years, and Loop and colleagues [3] had a median follow-up of 2.1 years. Finally, Braxton and colleagues [4] had a mean follow-up of 4.1 years, while Ståhle and colleagues [6] had a mean follow-up of 5 years. Without any doubt, to our knowledge, our longitudinal cohort study has the longest median follow-up time of all studies published until now.

On the other hand there is a concordance in the estimated hazard of mediastinitis on mortality between our study and the others. Our crude rate ratio of the effect of mediastinitis on mortality was 2.01, 95% CL (1.49 and 2.74). Milano and colleagues [1] had 2.2 to 2 years, while Loop and colleagues [3] had a rate ratio of 3.4 at 3 years and Ståhle and colleagues [6] had a rate ratio of 2.4 at 5 years follow-up.

Also, there was a concordance in the adjusted hazard ratio for multiconfounders estimate. We had a hazard ratio of 1.59, 95% CL (1.16 and 2.55). This was close to the adjusted hazard rate of Ståhle and colleagues [6] of 1.90 (1.20 and 2.80), and to the estimate of Braxton and colleagues [4] 1.79 95% CL (1.30 and 2.19). The replication of the increased risk of mediastinitis on mortality in different geographic populations of CABG patients, and in different periods of time, is an indicator of the validity of this association.

Another original result confirming the consistency of this association is the finding that SMR for males with mediastinitis had an increased risk of mortality compared with males without mediastinitis when controlling for the total Norwegian population. The SMR for males without mediastinitis of 2.5, 95% CL (2.1 and 3.05) was the same as the SMR estimated by Risum and colleagues [28] (2.5, 95% CL [2.2 and 2.9] for males, considering a cohort of 1,025 patients operated between August 1982 to December 1986 (another time period) with a median follow-up of 7.4 years in Norway. These analyses were impossible to perform for females in our study.

There are some biologic mechanisms that can explain this excess risk of mediastinitis. Information is scarce with regard to the long-term graft patency in patients who develop mediastinitis. These patients have a long-standing chronic inflammatory process, which might influence negatively the graft patency. Inflammation can reduce plaque stability and increase thrombogenesis in both coronaries and grafts [29, 30].

Hypercholesterolemia may also play a role by activating the inflammatory reaction associated with accelerated progression of atherosclerosis [22]. These factors might contribute to explain the reduced long-term survival rate in CABG patients having mediastinitis.

Deep sternal wound infections may cause constrictive pericarditis. Even patients with mild constriction have a comprised left ventricular filling and decreased stroke volume and cardiac output. Pericardial, as well as epicardial, fibrosis after mediastinitis is thus another possible contributor to the observed excess long-term mortality [22, 29, 30].

Mediastinitis is a devastating complication after cardiac surgery and is associated with a significant reduced long-term survival. At 10.3 years follow-up these patients had a 59% higher mortality risk compared with the patients without mediastinitis, and mostly caused by cardiac deaths.

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