

# Effect of female gender on the outcome of coronary artery bypass surgery for left main coronary artery disease

*Sol ana koroner arter hastalığı nedeniyle koroner baypas geçiren olgularda kadın cinsiyetin prognoz üzerine etkisi*

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## ABSTRACT

**Objective:** Early mortality after coronary artery bypass grafting is generally higher in women than in men. This study analyzes the effect of female gender on early mortality of coronary artery bypass grafting particularly for left main coronary artery disease.

**Methods:** Study population consisted of 144 consecutive patients (33 women, 111 men) undergoing coronary artery bypass grafting for left main coronary artery disease. Mean follow-up was  $25.1 \pm 14.0$  months. Data were collected retrospectively and presented as mean  $\pm$  standard deviation. Survival analysis was done using Kaplan-Meier actuarial curve method with the log rank univariate test, followed by Cox's proportional rate multivariate model.

**Results:** Overall mortality was 7% in the patient population. Cox regression analysis revealed that the independent predictors of increased total mortality were female gender (HR 8.34, 95% CI 1.79 - 38.76,  $p=0.007$ ), advanced age (HR 1.12, 95% CI 1.02-1.23,  $p=0.014$ ), degree of left main coronary artery stenosis (HR 1.068, 95%CI 1.005-1.135,  $p=0.03$ ), and left ventricular ejection fraction (HR 0.93, 95% CI 0.87-0.99,  $p=0.03$ ). Female gender was found to be the only independent predictor of increased early mortality (HR 13.18, 95%CI 1.444-120.343,  $p=0.02$ ). After discharge from the hospital, female gender was no more a predictor of increased mortality.

**Conclusion:** According to these data, we may assume that female gender is related with increased mortality in coronary artery surgery for left main disease in the pre-discharge period however after discharge from hospital, long-term benefit of female survivors of coronary artery bypass grafting operated on for left main coronary artery disease might be as good as in men. (*Anadolu Kardiyol Derg 2007; 7: 134-9*)

**Key words:** Left main coronary artery disease, coronary artery bypass surgery, female gender, mortality, Kaplan-Meier analysis

## ÖZET

**Amaç:** Tüm koroner baypas operasyonları ele alındığında erken mortalite kadınlarda genellikle daha yüksektir. Bu çalışmada kadın cinsiyetin özellikle sol ana koroner arter hastalığı nedeniyle yapılan koroner baypas operasyonu sonrası erken dönem mortalite üzerine etkisi analiz edilmiştir.

**Yöntemler:** Çalışma popülasyonunu merkezimizde sol ana koroner arter hastalığı nedeniyle koroner baypas operasyonu geçiren ardışık 144 hasta (111 erkek, 33 kadın) oluşturmuştur. Veriler retrospektif olarak toplanmış ve ortalama  $\pm$  standart sapma olarak gösterilmiştir. Ortalama takip süresi  $25.1 \pm 14.0$  aydır. Sağkalım analizi Kaplan-Meier log rank tek-değişkenli test ve Cox çoklu regresyon model ile yapılmıştır.

**Bulgular:** Çalışma popülasyonunda toplam mortalite %7 olmuştur. Cox regresyon analizinde artmış total mortalitenin bağımsız öngördürücüleri olarak; kadın cinsiyet (HR 8.34, 95% CI 1.79 - 38.76,  $p=0.007$ ), ileri yaş (HR 1.12, 95% CI 1.02-1.23,  $p=0.014$ ), ana koroner arter hastalığının derecesi (HR 1.068, 95%CI 1.005-1.135,  $p=0.03$ ) ve düşük sol ventrikül ejeksiyon fraksiyonu (HR 0.93, 95% CI 0.87-0.99,  $p=0.03$ ) tespit edildi. Çalışmamızda kadın cinsiyet, artmış erken mortalitenin tek bağımsız öngördürücüsü olarak saptanmıştır (HR 13.18, 95%CI 1.444-120.343,  $p=0.02$ ). Hastaneden taburculuk sonrası dönemde kadın cinsiyetin mortalite üzerine bir etkisi kalmamıştır.

**Sonuç:** Taburculuk öncesi erken dönemde, sol ana koroner arter hastalığı nedeniyle koroner baypas operasyonu geçiren hastalarda kadın cinsiyet artmış mortalitenin bağımsız bir öngördürücüsü olabilir; ancak taburculuk sonrası uzun dönemde bu hasta grubunda kadınlar da operasyondan erkekler kadar faydalanıyor gibi görünmektedirler. (*Anadolu Kardiyol Derg 2007; 7: 134-9*)

**Anahtar kelimeler:** Sol ana koroner arter hastalığı, koroner baypas cerrahisi, kadın cinsiyet, mortalite, Kaplan-Meier analizi

## Introduction

Left main coronary artery (LMCA) disease which carries an ominous prognosis (1, 2) constitutes approximately 5-20% of patients undergoing coronary artery bypass grafting (CABG)

surgery (3-5) and CABG surgery has proven benefit over medical therapy during the follow-up of LMCA disease (6-8).

In patients undergoing CABG surgery, there is considerable controversy about the effect of gender on the outcome of operation. Female gender is found to be associated with

increased early mortality in several trials (9-12). However, there are also reports indicating that there is no significant difference in early mortality during the course of CABG surgery with respect to gender, when other risk factors are taken into consideration (13-16).

The aim of our study is to evaluate the independent effect of female gender, if any, on the outcome of patients undergoing CABG for LMCA disease. Evaluation is performed considering early, late and total mortality.

## Methods

### Patient group

Among the 1897 cases of CABG surgery in the cardiovascular surgery department in our institution between January 1999 and January 2004, one hundred and sixty patients who had presence of LMCA stenosis, defined by a reduction of the arterial lumen by more than 50%, constituted the initial study population. Six LMCA disease cases of re-do CABG surgery and eight patients (2 female, 6 male), whose follow-up data were not accessible during the data retrieval, were excluded from the study. Three of these patients' hospital records were missing and in five patients either the phone number record was wrong or the patient was moved to an unknown address. A total of 14 patients were excluded from the study because of these reasons. Remaining 144 patients constituted the final study population. All operations were performed by the same operating staff.

### Patient Characteristics

Patient characteristics and operation variables were retrieved from medical records and computer files in the Departments of Cardiovascular Surgery and Cardiology, Başkent University Faculty of Medicine Adana Hospital. The collected information described age, sex, presence of major risk factors (diabetes mellitus, hypertension, smoking habits, and hyperlipidemia), body surface area (BSA), presence or absence of unstable symptoms prior to admission and during hospitalization and prior myocardial infarction.

In all patients resting 12 lead surface electrocardiograms (ECG) and basal echocardiographic records before or on the day of coronary angiography were obtained from the patient files. Presence of preoperative arrhythmia and/or bundle branch block was assessed by the ECG recordings. Left ventricular ejection fraction was determined by two-dimensional echocardiography using modified Simpson's method. Selective coronary angiography was undertaken using the Judkins femoral or brachial approach, with a minimum of three views (right anterior oblique, left anterior and left lateral). All of the angiograms were assessed by a team of two separate cardiologists and one cardiovascular surgeon, and percent stenosis of LMCA was confirmed by all three physicians. The precise lesion topography (ostial, mid, and distal) and the presence of stenotic lesions in other coronary arteries were also determined by the same team separately. The right and left anterior descending and circumflex coronary arteries, respectively, including their branches were considered as one vessel each, whatever the number of obstructed side branches.

In patients undergoing CABG surgery, database was analyzed for the time interval between coronary angiography to surgical procedure, the number and types of grafts, extracorporeal circulation time, aortic clamp time and concomitant surgical procedures such as mitral valve replacement or carotid endarterectomy.

Long-term follow up was achieved by sending questionnaires to the patients, their physicians and their cardiologists. If there was no response to the questionnaires, further inquiries were made by telephone. Records of any past hospital admissions were evaluated. Finally, in the absence of any response to our inquiries, the possibility that the patient had died was checked with the death registry administration. Early mortality was defined as mortality during hospital admission or within one month after hospital discharge. Late mortality was defined as death after this time. Mean follow-up was  $25.1 \pm 14.0$  months.

### Operative Technique

After premedication with 0.1 mg/kg intramuscular morphine sulfate and 10 mg oral diazepam, anesthesia was induced with 0.05 mg/kg midazolam, 2 mg/kg fentanyl, 0.3 mg/kg etomidate, and 0.1 mg/kg vecuronium. Anesthesia was maintained with 0.5% isoflurane and 50% N<sub>2</sub>O in O<sub>2</sub>. Doses of fentanyl 2 mg/kg and vecuronium 0.05 mg/kg were administered as required. Patients who were operated under cardiopulmonary bypass were subjected to the same anesthetic and surgical protocols. Cardiopulmonary bypass was performed using a membrane oxygenator with prime volumes of 35 ml/kg. Pump flow and hematocrit were maintained at 2.5 to 3.0 L min/m<sup>2</sup> and 30%, respectively. The standard cardiopulmonary bypass procedure under moderate hypothermia (32°C) was performed in all patients. Perioperative fluid therapy and blood transfusions were administered according to changes in central venous pressure. Off-pump surgery patients were operated using commercially available devices applying pressure and suction. Choice of the type of procedure was made by one of the two individual surgeons appointed for the case. After surgery, each patient was returned to the cardiothoracic intensive care unit while still intubated and on ventilatory support.

Operations were classified as emergent, urgent or elective with respect to the time interval between coronary angiography and operation. An emergent operation was defined as the direct transfer of the patient from the catheterization laboratory to the operating room. Urgent operation was defined as the operation being performed before discharge following coronary angiography. All other operations were classified as elective.

The study was approved by the institutional ethics and research review committee.

### Statistical Analysis

Statistical processing was performed with the SPSS for Windows software (version 9.0, Chicago, IL, USA). Data are given as mean  $\pm$  SD for numerical variables. In the initial univariate analysis we used Pearson's  $\chi^2$  test or Fisher's exact test for categorical variables and Student's t test for numerical variables. As a second step, a survival analysis was done using Kaplan-Meier actuarial curve method with the log rank univariate test, followed by Cox's proportional rate multivariate model. The significance threshold was set at  $p < 0.05$  for all data.

## Results

### Population Characteristics

Study population consisted of 144 patients (33 women, 111 men) undergoing CABG surgery for LMCA disease.

Patients with LMCA disease constituted 8.4% of all patients undergoing CABG surgery. Comparison of age, preoperative risk

factors, clinical presentation, and angiographic features between men and women are shown in Tables 1 and 2.

Mean age of the patient group was 62±0.8 years. There was no difference with respect to age, BSA, left ventricular ejection fraction (LVEF) and presence of prior myocardial infarction, diabetes mellitus, smoking and hyperlipidemia between two genders in the study population. Hypertension was more frequent among women (27 women, 81.5% vs. 58 men, 52.7%; p=0.002). Atrial fibrillation was present in 10 men (9%) and none of the women preoperatively.

Angiographic features of the study population revealed no difference in the degree of percent stenosis in LMCA between men and women. The LMCA was totally occluded in 3 patients (1 woman, 2 men). Isolated LMCA stenosis was present in 10 patients (4 women, 12% vs. 6 men, 5%; p>0.05). Presence of an ostial lesion was more frequently seen among women than men (8 women, 24% vs. 9 men, 8%; p=0.026).

There was no emergent operation in the study group. There were 5 urgent cases (15.1%) in the female patients and 16 urgent cases (14.4%) in male patients. All other cases were electively operated.

Left internal mammarian artery graft was used in all cases. Twenty eight patients received total arterial revascularization (4 women, 12% vs. 18 men, 16%; p>0.05). Number of grafts per operation was 3.3±1.1 in the entire population and this parameter was not different between men and women (women 3.28±1.2 vs men 3.48±1.0; p>0.05). Also, use of off-pump surgery, total extracorporeal circulation time and cross clamping time was not different among women and men (Table 3). Three patients (1 woman, 2 men) received mitral valve replacement and another 3 patients (1 woman, 2 men) undergone carotid endarterectomy concomitantly during coronary artery bypass grafting.

**Follow-up**

The mean follow-up duration in January 2004 was 25.1±14.0 months. During the follow up period 5 patients admitted to

**Table 1. Preoperative population characteristics**

Variables	Women (n=33)	Men (n=111)	p
Age, years	62.3±7.5	61.8±8.9	0.74
Hypertension, n (%)	27 (81.5)	58 (52.7)	0.002
Diabetes mellitus, n (%)	12 (36)	35 (32)	0.37
Hyperlipidemia, n (%)	22 (66.7)	60 (54.1)	0.38
Smoking, n (%)	10 (30)	76 (69)	<0.001
Family history, n (%)	13 (39)	33 (30)	0.2
BSA, m <sup>2</sup>	28.8±7.1	27±4.0	0.34
Ejection fraction, %	46.7±9.4	47.9±10.9	0.53
Previous MI, n (%)	17 (51)	56 (50.5)	0.28
Angiography to operation time, days	15.2±17.3	10.8±13.1	0.41
Urgent operation, n (%)	5 (15.1)	16 (14.4)	0.61
Acute coronary syndrome, n (%)	10 (30)	31 (28)	0.29
Preoperative ECG Findings			
Sinus rhythm, n (%)	33 (100)	101 (91)	0.07
Atrial fibrillation, n (%)	0 (0)	10 (9)	0.07

BSA- body surface area, ECG- electrocardiogram, MI- myocardial infarction

**Table 2. Angiographic features**

Variable	Women (n=33)	Men (n=111)	p
LMCA stenosis 50%-70%, n (%)	22 (66.7)	53 (47.7)	0.59
LMCA stenosis 71%-90%, n (%)	8 (24.2)	38 (34.2)	0.43
LMCA stenosis 91%-99%, n (%)	2 (6.1)	18 (16.2)	0.12
LMCA stenosis 100%, n (%)	1 (3)	2 (1.8)	0.26
Ostial lesion, n (%)	8 (24)	9 (8)	0.018
Mid lesion, n (%)	8 (24)	52 (47)	0.016
Distal lesion, n (%)	17 (52)	50 (45)	0.48
Isolated LMCA stenosis, n (%)	4 (12)	6 (5)	0.37
LMCA+1 vessel, n (%)	2 (6)	11(10)	0.78
LMCA+2 vessel, n (%)	3 (9)	12 (11)	0.51
LMCA+3 vessel, n (%)	24 (73)	82 (74)	0.32

LMCA- left main coronary artery

hospital for decompensated heart failure (1 woman, 3.03% vs. 4 men, 3.6%;  $p>0.05$ ); 3 patients for stroke (1 woman, 3.03% vs. 2 men, 1.8%;  $p>0.05$ ); and 15 patients for myocardial infarction or unstable angina pectoris (3 women, 9.0% vs. 12 men, 10.1%;  $p>0.05$ ).

**Mortality**

The overall mortality at the end of the follow-up was 7.0%. The overall mortality was higher among women in the surgically treated group (5 women, 15.6% vs 5 men, 4.6%,  $p=0.049$ ). Log rank test for survival revealed a higher overall mortality for women ( $p=0.013$ ) (Fig. 1), however late mortality did not differ significantly between the genders ( $p=0.814$ ).

Cox regression analysis revealed that the independent predictors of increased total mortality were female gender (HR 8.34, 95% CI 1.79 - 38.76,  $p=0.007$ ), advanced age (HR 1.12 95% CI 1.02-1.23,  $p=0.014$ ), degree of LMCA stenosis (HR 1.068, 95%CI 1.005-1.135,  $p=0.03$ ), and LVEF ( HR 0.93, 95% CI 0.87-0.99,  $p=0.03$ ) showing that every 1% increase in LVEF results in approximately 7% risk reduction for the patient (Table 4). This reflects a strong association, approaching almost 9 fold increased risk for early mortality if one has the female gender when compared with men. In other words, being women yields an approximately 9 fold increased risk of early postoperative death when compared with men in population like ours, according to our results.

Early mortality was higher among women (4 women, 12.5% vs 1 man, 0.9%;  $p=0.01$ ). Two patients died immediately following the operation due to refractory low cardiac output state. One patient, the only man who died in the early period, died on the 9th postoperative day because of refractory low cardiac output state. This patient who has prior anterior myocardial infarction in his past medical history, also had undergone carotid endarterectomy together with coronary artery bypass grafting. One patient died on the 24th postoperative day due to massive gastrointestinal bleeding. One patient died on the 28th postoperative day because of mediastinitis. Two of the female patients who died in the early post-operative period were diabetic and one of them had total occlusion of LMCA. All of the

four female patients who died in the early postoperative period had also prior anterior myocardial infarction in their past medical history. Cox regression analysis revealed female gender as the only independent predictor of early postoperative mortality (HR 13.18 95%CI 1.444-120.343,  $p=0.02$ ). None of the patients who died in the early postoperative period had undergone postoperative coronary angiography. None of these patients had a postoperative myocardial infarction.

Late mortality was 3.5% (1 woman, 3% vs. 4 men, 3.6%  $p=ns$ ). Two patients died of sudden cardiac death, one after 13 months, and the other after 19 months following the operation. One patient died of intracranial bleeding secondary to traffic accident after 38 months following the operation. One patient, who also had undergone mitral valve replacement together with CABG, died of cerebrovascular accident after 39 months following the operation. One patient died of end-stage heart failure refractory to treatment after 61 months following the operation. Cox regression analysis revealed advanced age as the only independent predictor of late mortality (HR 1.374, 95%CI 1.106-1.707;  $p=0.004$ ).

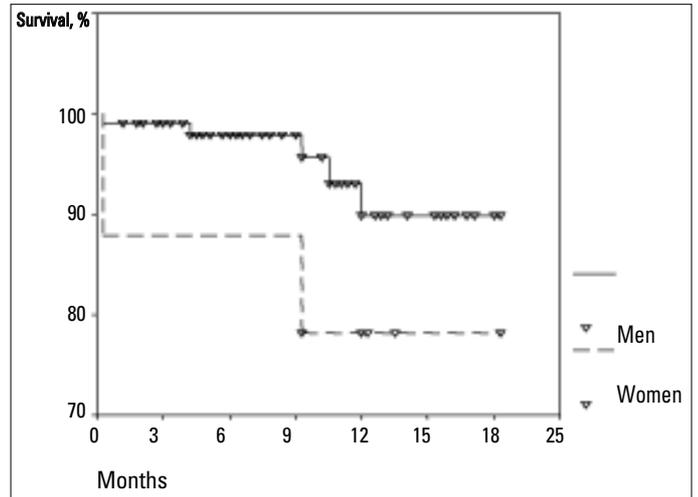


Figure 1. Two-year Kaplan-Meier survival curve in men and women, respectively (15.6% women vs 4.6% men,  $p=0.013$  in Log rank test)

Table 3. Intraoperative risk profile

Characteristics	Women	Men	p
Graft number, n	3.28±1.2	3.48±1.0	0.35
Cross-clamp time, min	55.6±25.7	56.3±20.01	0.83
Total pump time, min	87.3±42.1	86.9±30.2	0.69
Beating heart, n (%)	4 (12)	8 (7)	0.28
Full arterial graft, n (%)	4 (12)	18 (16)	0.78

Table 4. Multivariate Cox proportional hazard estimates

Variable	HR	95% CI	p
Female gender	8.34	1.79 - 38.76	0.007
Low EF	0.93	0.87-0.99	0.03
Advanced age	1.12	1.02-1.23	0.014
Degree of LMCA stenosis	1.068	1.005-1.135	0.03

CI- confidence interval, EF- ejection fraction, HR - hazard ratio, LMCA- left main coronary artery

## Discussion

This study revealed that female sex in a multivariate analysis may be an independent predictor of early mortality in the group of patients undergoing CABG surgery due to LMCA disease. However, during a follow-up period of 25.1±14 months after discharge, female gender was no more a predictor of increased mortality in this study. Female gender was remained as an independent predictor of total mortality because of the excess mortality in the early period.

There was no significant difference between two genders among age, ejection fraction, prior myocardial infarction, degree of LMCA stenosis, clinical presentation, BSA, diabetes mellitus and extent of coronary artery disease; reflecting a similar risk profile between two genders preoperatively. Females were found to be older in several series of patients undergoing CABG (5, 17, 18) none of these publications had a focus on especially LMCA disease patients with respect to gender. Although female patients were older in our study, difference between two genders did not reach statistical significance (women, 62.3 ± 7.5 vs. men, 61.8 ± 8.9). Hypertension was found to be more frequent among women, and smoking was more frequent among men similar to several series of CABG patients (5, 17, 18). Among the angiographic features of patients only the presence of an ostial lesion was found to be more frequent in female patients (24% vs. 8%; p=0.026). This lesion morphology was also found more frequent among women in a previously published data and this morphology had no effect on the outcome of patients in that study (19). Lesion morphology was not a predictor for increased mortality in our study reflecting a similar result.

Various factors at operation including the urgency of operation, number of grafts, cross-clamping time, extracorporeal circulation time, percent of off-pump surgery, percent of internal mammary artery use and total arterial revascularization was not different between two sexes at our center among patients undergoing CABG surgery for LMCA disease.

Although various preoperative characteristics such as age, ejection fraction, BSA, unstable clinical presentation, diabetes mellitus and extend of coronary artery disease, that can be assumed to influence the early mortality, were similar among two genders in our population; early mortality was still higher in women. Cox regression analysis defined female gender as an independent predictor of early mortality among patients undergoing CABG surgery for LMCA disease.

Late mortality was not different among two sexes during a follow-up period of approximately 2 years. Graft patency in the long-term is superior when internal mammary artery (IMA) grafts are used compared with venous grafts (20) at our institution use of an IMA graft is routine whenever possible and there is no difference in IMA utilization between two genders. In a previous study (19), increased cross clamping time was found to be a predictor of increased coronary events including mortality in patients undergoing CABG for LMCA disease and extracorporeal circulation time was very close to be significant as such a predictor. There was not a significant difference among cross clamping time and extracorporeal circulation time between two genders and these parameters were not found as significant predictors of early or late mortality in our study.

Age was found to be the only independent predictor of late mortality in our patient population. Influence of age on the late outcome of patients undergoing CABG is consistent with several previous studies (18, 21).

Several previous investigations concerning this issue had outlined data, derived from a population undergoing CABG, however none has focused merely on LMCA disease. In these studies, which revealed a higher mortality in female gender, authors explain this finding with decreased body size and smaller coronary arteries in female patients however this explanation is not valid in our research as both gender groups have similar BSA values (15, 22-24).

This was a retrospective study with all the biases inherent in that type of study. We retrospectively collected data from a population of patients operated on for LMCA disease, without any randomization and control group. The small sample size is the main limitation in our study. Due to the difficulty to establish a study population in such a specific patient group who has been undergoing CABG operation, we were not able to increase the sample size any further. This resulted in the relatively low number of events observed (mortality) and a relatively large range of confidence interval in the calculated result. Nevertheless, this study may be accepted as informative rather than conclusive in the understanding of LMCA disease with a focus on female patients undergoing CABG surgery.

This study revealed that female sex in a multivariate analysis may be an independent predictor of early mortality in the group of patients undergoing CABG surgery due to LMCA disease. However, during a follow-up period of 25.1±14 months after discharge from the hospital, female gender was no more a predictor of increased mortality. In other words, long-term benefit of female survivors of CABG surgery patients operated on for LMCA disease might be as good as in men. This issue warrants further studies with larger sample size in order to reach a conclusion.

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