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Female sex is associated with increased mortality and morbidity early, but not late, after coronary artery bypass grafting

G. Brandrup-Wognsen*, H. Berggren*, M. Hartford, Å. Hjalmarson, T. Karlsson and J. Herlitz

Divisions of Thoracic and Cardiovascular Surgery, and Cardiology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden*

Objective To describe mortality and morbidity during a period of 2 years after coronary artery bypass grafting in relation to gender.

Design Prospective follow-up study.

Setting Two regional cardiothoracic centres which performed all the coronary artery bypass operations in western Sweden at the time.

Subjects A total of 2129 (1727 (81%) men and 402 (19%) women) consecutive patients undergoing coronary artery bypass surgery between June 1988 and June 1991 without concomitant procedures.

Results Females were older and more frequently had a history of hypertension, diabetes mellitus, congestive heart failure, renal dysfunction and obesity. In a multivariate analysis, taking account of age, history of cardiovascular diseases and renal dysfunction, female sex appeared as a significant independent predictor of mortality during the 30 days after coronary artery bypass grafting ($P<0.05$), but not thereafter.

Various postoperative complications including neurological deficit, hydro- and pneumo-thorax, perioperative myocardial damage and the need for assist devices and prolonged reperfusion were more common in females than males.

Conclusion Females run an increased risk of early death and the development of postoperative complications after coronary artery bypass surgery as compared with males. Late mortality does not appear to be influenced by gender and the long-term benefit of the coronary artery bypass graft operation is similar in men and women.
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Key Words: Aortocoronary bypass, mortality, morbidity, gender.

Introduction

Coronary artery bypass grafting remains the most commonly used form of myocardial revascularization, but the clinical profile of the patients has changed. Today, patients undergoing coronary artery bypass grafting are older with more associated diseases[1]. In spite of this, the elective coronary artery bypass operation is performed with a low early mortality, which is partly explained by perioperative improvements in areas such as anaesthetic and surgical management and myocardial protection[2]. Women still run a greater risk of in-hospital mortality than men. This has been found in several studies throughout the years[3–7]. However, the prognosis in the somewhat longer term after coronary artery bypass grafting in relation to gender has not been as carefully evaluated. One exception is the large Coronary Artery Surgery Study[8], but they enrolled patients between 1974 and 1979.

This study aims to describe the clinical course, in a coronary artery bypass population from 1988–1991, during 2 years of follow-up in relation to gender.

Methods

Between June 1988 and June 1991, all the patients from western Sweden on whom coronary artery bypass

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Correspondence. Dr Gunnar Brandrup-Wognsen, Division of Thoracic and Cardiovascular Surgery, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden.

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grafting was performed without concomitant surgical procedures at the department of Thoracic and Cardiovascular Surgery at Sahlgrenska University Hospital and at the Scandinavian Heart Center in Göteborg were registered prospectively. These two hospitals performed all the coronary artery bypass operations in the western health care region of Sweden at the time. The region serves a population of about 1 600 000.

Perfusion was performed using a roller pump (Jostra [Gambro, Lund, Sweden] or Sarns [3M, Ann Arbor, MI, U.S.A.]) set-up with the patient, with few exceptions, in moderate hypothermia (28–34 °C rectal temperature). A variety of oxygenators were used: 50% of the oxygenators were Gambro G10 (Gambro, Lund, Sweden). These were used until November 1988. The other oxygenators, used throughout the study period, were Cobe CML (Cobe Laboratories Inc., Lakewood, CO, U.S.A.), Medtronic Maxima (Medtronic, Anaheim, Ca, U.S.A.) and Sarns GSO I (3M, Ann Arbor, MI, U.S.A.).

Anaesthesia was induced with thiopentone and fentanyl, followed by pancuronium and continued with a combination of nitrous oxide and the intermittent administration of a volatile anaesthetic. Myocardial preservation was achieved with a hyperkalaemic, hypothermic crystalloid solution (modified St Thomas) and external cooling was established with ice slush or a cold saline solution. The myocardial temperature was usually monitored and kept under 15 °C. In the arrested heart, the distal anastomoses were performed first, using a monofilament suture with a continuous running suture technique, and the aortic anastomoses were performed over a partial occluding clamp during reperfusion of the heart and while re-warming the patient.

A history of myocardial infarction, congestive heart failure, hypertension, diabetes mellitus, cerebrovascular disease and intermittent claudication prior to the operation was based on patient information and medical records.

The formula which estimates creatinine clearance based on serum creatinine to describe renal function was adapted from Cockcroft and Gault[9]. Renal dysfunction was defined as creatinine clearance below 60 ml . min^{-1}. Obesity was defined as Body Mass Index >30 kg . m^{-2}[10]. The left ventricular ejection fraction was estimated from a contrast ventriculogram in the right anterior oblique projection.

The study population was divided into six groups according to the urgency of the operation. Waiting-list patients without priority and those who were in hospital waiting for an operation were considered elective. Acute operations comprised: those patients who were sent for an operation with a diagnosis of unstable angina pectoris with ongoing nitroglycerine infusion or thoracic epidural anaesthesia; those sent for an immediate operation due to failed coronary angiography (due to impending myocardial infarction and/or haemodynamic instability) or percutaneous transluminal coronary angioplasty; those sent for an operation while developing an acute myocardial infarction; or those sent for an operation with ongoing ventricular fibrillation.

All the patients were interviewed by a member of the research team prior to the operation. Information about their previous history was noted from this interview and retrieved from the hospital medical records.

Definitions of postoperative complications

Re-operation. Re-operation due to bleeding, suspected tamponade or graft occlusion.

Neurological complications. All patients with a positive neurological consultation report were considered to have had a neurological complication. These included all changes in the brain verified by computed tomography to clinically-suspected changes.

Pneumothorax. X-ray verified pneumothorax leading to treatment with chest drainage.

Supraventricular arrhythmias. Atrial fibrillation or flutter leading to the administration of antiarrhythmics or cardioversion.

Inotropic drugs. Dopamine or corresponding drugs in doses of $\geq 6\ \mu g \cdot kg^{-1} \cdot min^{-1}$.

Circulatory assist devices. Intra-aortic balloon pump, extracorporeal membrane oxygenation, left ventricular assist device and right ventricular assist device. The intra-aortic balloon pump was not used preoperatively in our hospitals at this time.

Perioperative myocardial injury. An elevation in serum-aspartate aminotransferase (S-ASAT, EC 2.6.1.1 {normal range $<0{\cdot}7\ \mu kat \cdot L^{-1}$}) to $>2{\cdot}0\ \mu kat \cdot L^{-1}$ within 48 h after the operation.

All complications were defined as those whose onset occurred during the hospital stay. Information on deaths was obtained from the Swedish National Registry of Deaths. Information on deaths reaches this registry within 14 days of the date of death. Survival confirmation was obtained from the Swedish Population Registration System and all the patients who were still alive were sent a questionnaire 3 months, 1 year and 2 years after the operation. They were asked whether they had been rehospitalized after the operation and at which hospital. Furthermore, the medical records from the referring hospitals were checked during the 2 years after the operation. Information about rehospitalization in a hospital other than the referring hospital is usually available from the referring hospital.

During the 2 years of follow-up, acute myocardial infarction was defined if two of the following three criteria were fulfilled: (1) pain suggesting acute myocardial infarction of at least 15 min duration; (2) elevated serum enzyme activity indicating acute myocardial infarction; (3) development of Q-waves in at least two leads on a 12-lead standard electrocardiogram. Stroke was defined as the development of neurological deficit with a duration of more than 24 h.

Transient ischaemic attack was defined as the development of neurological deficit with a duration of less than 24 h and postpericardiotomy syndrome was defined as the constellation of fever, elevated

Table 1 Baseline characteristics

	Males (n=1727)		Females (n=402)		P*
	n	%	n	%	
Age, mean (median)	62·3	(63)	64·3	(66)	<0·0001
History of:					
Myocardial infarction (1/0)†	1077	64	222	55	<0·01
Angina pectoris (0/0)	1686	98	390	97	
Congestive heart failure (2/0)	250	14	75	19	<0·05
Hypertension (2/2)	578	34	199	50	<0·0001
Diabetes mellitus (2/0)	201	12	67	17	<0·01
Renal dysfunction (4/1)	379	22	211	53	<0·0001
Cerebrovascular disease (1/0)	147	9	31	8	
Intermittent claudication (3/0)	199	12	61	15	
Obesity (0/0)	194	11	70	17	<0·01
Smoking (9/4)	1296	75	196	49	<0·0001
Percutaneous transluminal coronary angioplasty (1/0)	83	5	28	7	
Coronary artery bypass grafting (1/0)	97	6	19	5	
Three-vessel disease (82/13)	1092	66	245	63	
Ejection fraction <40% (130/38)	151	9	27	7	

*P value denoted if $P<0·05$. †Number of patients with missing information.

Table 2 Degree of urgency of operation

	Males (n=1727)		Females (n=402)	
	n	%	n	%
Elective operation	1355	78	301	75
In hospital waiting for operation	209	12	63	16
Sent for operation with a diagnosis of unstable angina pectoris with ongoing nitroglycerine infusion or thoracic epidural anaesthesia	112	6	25	6
Sent for immediate operation from coronary angiography or percutaneous transluminal coronary angiography	28	2	9	2
Sent for operation while developing an acute myocardial infarction	15	0·9	4	1·0
Sent for operation with ongoing ventricular fibrillation	8	0·5	0	0

$P=0·51$ and refers to the overall distribution of patients.

sedimentation rate, pleural effusion, pericardial effusion, tiredness and pain.

Statistical methods

Fisher's permutation test was used to test for difference between sex and other variables, except for mortality where the log rank test was used. Cox's proportional hazards model was used for multivariate analysis. All *P* values are two-sided and have not been corrected for multiple comparisons.

Results

In a consecutive series of 2365 patients, 2129 fulfilled the inclusion criteria, of whom 402 (19%) were females.

The baseline characteristics in Table 1 show that females differed from males by being older, more frequently having a history of congestive heart failure, hypertension, diabetes mellitus, renal dysfunction and obesity, and less frequently having a history of myocardial infarction and smoking. The degree of urgency of operation did not differ significantly between males and females (Table 2).

When it came to surgical procedures there was no difference between the two groups, apart from the fact that males received more grafts than females (a mean of 3·8 compared with 3·6; $P<0·01$) (Table 3). Note that women received an internal mammary artery graft just as often as men.

Several postoperative complications were more frequent among females. They included neurological complications, pneumo- and hydrothorax, serum-aspartate aminotransferase $>2·0\ \mu kat \cdot L^{-1}$ and the need for any of the following: inotropic drugs, prolonged reperfusion in a heart–lung machine and the use of assist devices (also shown in Table 3).

During the first 30 days, mortality was 2·8% in males vs 7·0% in females ($P<0·0001$) (Table 4, Fig. 1). However, late mortality did not differ significantly between the genders. The total 2-year mortality was 6·5% in males and 11·8% in females ($P<0·001$). In a multivariate analysis taking age, sex, history of cardiovascular dysfunction and renal dysfunction into account, female sex appeared as an independent predictor of mortality for 30 days after coronary artery bypass grafting ($P<0·05$) but not thereafter.

As is also shown in Table, 4, various aspects of morbidity, including the development of acute myocardial infarction, stroke, transient ischaemic attack and suspected postpericardiotomy syndrome, were seen with a similar frequency in males and females.

Females required more days in hospital than males during the 2 years of follow-up ($P<0·001$) (Table 5). This was mainly due to a longer mean duration of hospitalization associated with the primary operation ($P<0·0001$) and a greater need for rehospitalization after initial discharge due to complication associated with the primary operation ($P<0·01$). The need for rehospitalization for other reasons was similar in males and females.

In Table 6, the place and mode of death is shown. When all the patients were included in the analysis, the proportion of deaths in hospital was higher among females than males. The same thing applied to deaths due to stroke.

Table 3 Surgical procedures and postoperative complications

	Males (n=1727)		Females (n=402)		*P**
	n	%	n	%	
Surgical procedures:					
Aortic cross-clamp time (mean; min) (5/0)†	54·0		52·8		
Number of grafts (mean) (5/0)	3·8		3·6		<0·01
Mean aortic occlusion time per distal anastomosis (min) (6/0)	15·0		15·5		
Internal mammary artery (4/0)	1357	79	307	76	
Endarterectomy (11/0)	127	7	29	7	
Postoperative complications:					
Re-operation (7/0)	115	7	33	8	
Neurological complications (11/1)	58	3	24	6	<0·05
Pneumo/hydrothorax (11/1)	86	5	32	8	<0·05
Supraventricular arrhythmias (11/1)	481	28	108	27	
Inotropic drugs (9/0)	289	17	105	26	<0·0001
Prolonged reperfusion in heart–lung machine (11/0)	24	1	14	3	<0·01
Assist device (10/0)	35	2	24	6	<0·001
Serum-aspartate aminotransferase >2·0 μkat . L^{-1} (25/8)	432	25	140	36	<0·001

*P value denoted if $P<0·05$. †Number of patients with missing information

Table 4 Mortality and morbidity during 2 years of follow-up

	Males (n=1727)		Females (n=402)		*P**
	n	%	n	%	
Mortality:					
<30 days	48	2·8	28	7·0	<0·0001
30 days–2 years	64	3·8	19	5·1	
2 years (total)	122	6·5	47	11·8	<0·001
Morbidity:					
Development of acute myocardial infarction (5/1)†	36	2·1	12	3·0	
Development of transient ischaemic attack (5/1)	17	1·0	6	1·5	
Development of stroke (5/1)	51	3·0	10	2·5	
Suspected postpericardiotomy syndrome (7/2)	68	4·0	22	5·5	

*P value denoted if $P<0·05$. †Number of patients with missing information.

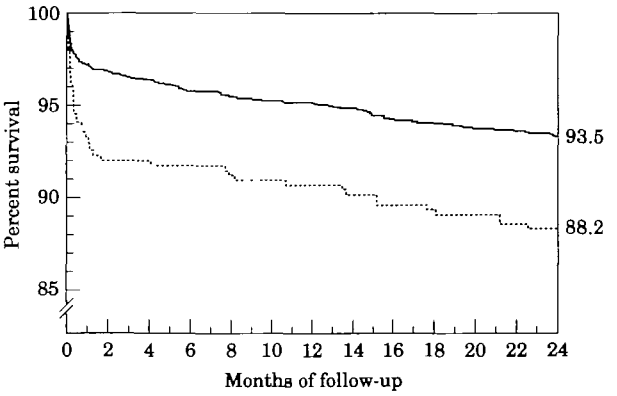

***Figure 1* Two-year survival in men and women respectively (Kaplan–Meier). ———, males; ····, females. $P=0·0002$.**

Discussion

This prospective study, which included a consecutive series of all the patients undergoing coronary artery bypass grafting in a well-defined area during a period of 3 years (patients undergoing concomitant procedures such as valve replacement, septal defect repair or aneurysmectomy were excluded), compares the outcome for males and females during 2 years of follow-up. It shows that female sex in a multivariate analysis is a powerful determinant of early mortality but that the long-term survival among women is as good as in men. Mortality during the first 30 days was 2·5 times as high in females as in males. These results are similar to the results in other studies throughout the years[6,8,11].

Females were older than males more frequently and had a previous history of diabetes and hypertension, diseases found to be major risk indicators of coronary artery disease in women[12,13]. Similar observations have been made before[6,11], but the observation that females more frequently displayed signs of renal dysfunction has not been reported as clearly in the past. To some extent this might be explained by their higher age and more frequent history of hypertension, diabetes mellitus and preoperative congestive heart failure.

Greater adverse preoperative characteristics, such as women being older and having more associated diseases, have been suggested as one explanation of the

Table 5 Number of days in hospital during a period of 2 years after coronary artery bypass surgery

	Males (n=1727¶)			Females (n=402)			P§	
	%*	median†	mean‡	%	median	mean	(%)	(mean)
Total including primary operation	100	16	23	100	20	27		<0·001
Associated with primary operation	100	14	15	100	16	18		<0·0001
After hospital discharge:								
Complications of primary operation	3	10	0·5	7	12	1·2	<0·01	<0·05
Postpericardiotomy syndrome	1	8	0·2	1	12	0·2		
Myocardial infarction	2	9	0·2	2	12	0·3		
Angina pectoris	11	6	1·1	11	8	1·2		
Chest pain (other cause)	8	3	0·4	7	4	0·5		
Heart failure	6	7	0·9	5	4	0·6		
Stroke	2	14	0·5	1	10	0·1		
Intermittent claudication	0·6	9	0·07	0·7	27	0·2		
Pulmonary embolism	0·4	8	0·04	1	7	0·1		
Infection	5	6	0·5	5	7	0·6		
Other reason	25	6	3	25	9	4		

*Percentage of patients who were hospitalized. †Median number of days in hospital among patients who were hospitalized. ‡Mean number of days in hospital among patients who were hospitalized. §P value denoted if $P<0·05$. ¶Information was missing for five males and one female.

Table 6 Place and mode of death

	Males (n=112)		Females (n=47)	
	n	%*	n	%
Place of death (0/0)†:				
In hospital	90	80	43	91
Outside hospital	22	20	4	9
Mode of death:				
Cardiac (0/0)	83	74	29	62
Myocardial infarction	51	46	17	36
Non-cardiac (0/0)	25	22	12	26
Stroke	8	7	7	15
Pulmonary embolism	2	2	1	2
Uncertain (0/0)	4	4	6	13
Symptoms associated with death (0/0)·				
Congestive heart failure	61	54	21	45
Cardiogenic shock	1	0·9	1	2
Electromechanical dissociation	0	0	0	0
Ventricular fibrillation	16	14	6	13

*Percentage of dead patients. †Number of patients with missing information.

higher mortality figures among women. However, since female sex was an independent predictor of death, discrepancies in preoperative characteristics can explain only part of the increased mortality among women.

Various factors at operation, including the degree of urgency, did not differ between the sexes at our centre. Previous studies have suggested that females more frequently have an acute presentation and that this causes part of the higher mortality rates among women[6,7,14]. The urgency factor did not contribute to the higher mortality among women in our material.

One operative factor which differed between men and women was that men received more bypass grafts per patient. If anything, this would have been expected to increase the risk of perioperative death in males. From a technical point of view, surgery is often more complicated in women because of their smaller body surface area, which is significantly associated with a smaller coronary vessel diameter as recently described[14]. Technical problems are another factor which has been discussed as a possible reason for females having a higher operative mortality following bypass surgery. However, the difference in mean time required to perform a distal anastomosis in men compared with women was small at our centre (mean time 15·0 min vs 15·5 min).

It has also been reported that the internal mammary artery is less frequently used in females than in males[11,15]. Graft patency in the long term is superior when internal mammary grafts are used compared with saphenous vein grafts[16]. At our institution, the use of the internal mammary artery graft is routine whenever possible, and there is no difference in mammary artery utilization between the genders.

Several complications, including indirect signs of perioperative myocardial damage, occurred at a higher frequency among females. These findings differ from those previously reported by others[4,17] and might explain some of the early excess mortality among females in our study.

Neither late mortality nor the development of acute myocardial infarction or stroke was significantly associated with gender. In terms of long-term mortality, these results are consistent with previous findings[4,15]. It is important to point out that the long-term benefit of female survivors of bypass surgery is as good as in men. In the evaluation of the mode of death, we found no indication that any specific type of death is more predominant among females. It has previously been

reported that, in the early phase females die more frequently in association with heart failure and haemorrhage[7]. Our data was, however, based on a limited sample size (only 47 deaths among females).

One major limitation in this study and other studies like it is that we do not know if we have a representative patient population. The prevalence of heart disease is lower among women compared with men[18] but it probably does not reflect the difference in the use of coronary bypass surgery any way[19].

In conclusion, our results in a consecutive series of patients from western Sweden show that female sex was one the most powerful preoperative predictors of early mortality. However, the long-term benefit of female survivors of bypass surgery was as good as in men.

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