Early results of coronary artery bypass graft surgery in women

Bronisław Czech¹, Ewa Kucewicz-Czech², Jerzy Pacholewicz¹, Jacek Wojarski¹, Jacek Puzio², Roman Przybylski¹, Arkadiusz Farmas¹, Bogdan Ryfiński¹, Marian Zembala¹

¹ Department of Cardiac Surgery and Transplantology, Medical University of Silesia, Silesian Center for Heart Diseases, Zabrze, Poland ² Department of Cardioanesthesiology, Medical University of Silesia, Silesian Center for Heart Diseases, Zabrze, Poland

Abstract

Background: Coronary artery disease is one of the leading causes of death among women in developed countries all over the world. Coronary artery bypass grafting (CABG) is a well established therapeutic modality to treat diffuse coronary artery atherosclerosis.

Aim: In this study we focused on the retrospective assessment of the early results of CABG in women as compared to the results of such treatment in men.

Methods: This analysis involved 2881 patients (677 women and 2204 men) who underwent CABG between 2003 and 2005. An operative technique (conventional on-pump or off-pump) was applied in a similar proportion of patients in both groups (on-pump: 59.4% of women and 59.6% of men; NS). Women were older than men and had higher body mass index. Concomitant disorders such as diabetes mellitus, hypertension and hypercholesterolaemia were noted more frequently in female patients.

Results: In the perioperative period, left ventricular failure requiring intra-aortic balloon pump insertion and administration of high doses of catecholamines was observed significantly more often in women than in men (22.1 vs. 16.1%, respectively; p < 0.001). Perioperative myocardial infarction was diagnosed more frequently in women (5.5 vs. 2.9%; p < 0.001). In female patients, the rate of repeat operation was higher (8.9 versus 5.1%; p < 0.001) and more subjects required blood transfusions (45.5 vs. 27.5%; p < 0.001). Female gender featured a higher rate of postoperative acute renal failure requiring renal replacement therapy (8.5 vs. 0.95%; p < 0.001). Mechanical ventilation was longer, and women stayed longer in the postoperative intensive care unit as well as in hospital. Early postoperative mortality among women was 3.6%, i.e. significantly higher than in male patients (1.6%) (p < 0.01). **Conclusions:** The analysis performed herein suggests that mortality and morbidity after CABG is higher in women than in men.

Key words: coronary artery disease, coronary artery bypass grafting, women, complications, mortality

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Introduction

In the past 40 years, the attention of cardiologists regarding the treatment of coronary artery disease (CAD) has been focused mainly on the group of male patients, markedly less on the female population. Incidence of CAD in the population aged 35-44 years is six times higher among men than women, while at the age of over 75 years it becomes similar, irrespective of patient gender [1]. Prevalence of CAD among young women is significantly lower than in older ones, and it

increases in the middle-aged female population. Woman develop symptoms of CAD 10 years later than men and at the time of the first myocardial infarction (MI) diagnosis they are usually older than men by an average of 20 years. Epidemiological studies confirmed a protective role of endogenous oestrogens in women at the premenopausal age [2]. Women with established diagnosis of CAD present with more risk factors than male patients. They are older, and more often suffer from diabetes mellitus and have congestive heart failure [3]. Angiograms of coronary arteries in females

Address for correspondence:

Ewa Kucewicz-Czech MD, Oddział Kliniczny Kardioanestezji i Intensywnej Terapii Pooperacyjnej, ŚIAM, Śląskie Centrum Chorób Serca, ul. Szpitalna 2, 41-800 Zabrze, tel./fax: +48 32 273 27 31, e-mail: kardanest@slam.katowice.pl **Received:** 20 September 2006. **Accepted:** 21 February 2007.

usually reveal advanced and diffuse form of atherosclerosis. This is the reason why females are more frequently reffered for urgent revascularisation procedures. On the other hand, 40% of women without clear clinical symptoms of CAD have atherosclerotic lesions detected in coronary angiography.

Atherosclerosis is a result of impaired function of endothelial cells and of microcirculation dysfunction [4]. Women have smaller hearts, smaller diameter of the coronary arteries and often subcritical, diffuse atherosclerotic lesions, in contrast to the typical male pattern with haemodynamically critical, isolated obstructive lesions confined mainly to the proximal segments of the coronary vessels [5]. Coronary artery disease is one of the leading causes of death among women in developed countries all over the world. One out of seven women currently living in Europe will die of CAD. In the UK more than 1.2 million women have an established diagnosis of CAD [6]. Detection of this disease in women is often a real challenge, requiring an enormous level of discernment because the clinical symptoms often differ from those described in the cardiology textbooks [5].

Watanabe et al. analysed the results of invasive therapy for CAD in a group of over 100 000 patients and documented that women who underwent percutaneous coronary intervention (PCI) had two-fold higher early mortality rate than male patients [7]. Women were more frequently referred for urgent coronary artery bypass grafting (CABG) than men [7, 8]. The total costs related to hospitalisation and associated with PCI were higher in a group of women than men [2].

A review of current literature by G.W. Mikhail indicated that women after PCI also had higher mortality [3]. The rate of postprocedural adverse events such as cerebral stroke, vascular complications and MI is higher among women than men. However, he casts doubt on higher mortality in females after adjusting for concomitant risk factors other than patient gender. Analysis of late results showed that restenosis rate was not gender-dependent and most current studies reveal that women after PCI benefit much more from the treatment than men in the long--term follow-up [3]. The results of treatment of either acute coronary syndromes or MI in women are controversial and suggest benefits only in the high--risk groups. However, these data were published before introduction of antimitotic stents into clinical practice and so further studies are mandatory in this group of patients. A possible explanation of worse results is smaller coronary vessel diameter as well as arterial wall more vulnerable for dissection and perforation [2].

Many reports indicated also higher mortality in women undergoing CABG procedures. It has been emphasised that women referred for CABG have more comorbidities, more often require urgent surgery, are older at the time of surgery and have smaller coronary vessel diameters. Less frequently the internal mammary artery is used in this group of patients. In the postoperative period more often ischaemic cerebral stroke, excessive bleeding, necessity of prolonged mechanical ventilation and heart failure are detected. However, the long-term benefits related to CABG are clear. Some studies showed that results of surgery in this subgroup of women were much better than in the male patient group [3, 9]. Female gender is associated with higher mortality in the subgroups of low and medium operative risk patients, although it does not have a negative impact on the results in the high-risk patients [9]. Some authors indicated a potential decrease in the rate of perioperative complications in women undergoing CABG using a beating-heart technique (off-pump) [6].

In the present study we retrospectively assessed early results of CABG in women as compared to the results of such treatment in men.

Methods

Patients

The analysis involved 2881 patients (677 women, 2204 men) who underwent CABG between 2003 and 2005. The period of clinical observation was confined to the hospitalisation period directly related to surgery. Patients who underwent concomitant surgical procedures such as valvular repair or replacement, correction of congenital malformation, ascending aortic aneurysm repair, etc., were excluded from this study.

In the examined group of patients, women were older than men, and had higher body mass index (BMI) and better left ventricular (LV) function. Comorbidities such as diabetes mellitus, hypertension and hypercholesterolaemia were seen more frequently among women. The burden of renal failure, peripheral artery atherosclerosis and chronic obstructive pulmonary disease was comparable in both patient groups. History of MI was significantly more frequent in men. Two or more previous MI were found in 13.5% of women and 20.5% of men referred for surgery. Rates of percutaneous or surgical revascularisation procedures in the past were similar in both groups (Table I).

Characteristics of procedures

The rates of elective, urgent and emergency operations did not differ between female and male patients. Women had higher operative risk as calculated

Table I. Demographic data and comorbidities with respect to gender				
Parameter	Women	Men	р	
Age [year] (mean)	63.5	60.3	<0.001	
BMI [kg/m²]	28.6	27.8	<0.001	
LVEF [%]	52.5	49.9	<0.001	
Previous myocardial infarction (one or more) [%]	49.3	59.7	<0.001	
Revascularisation procedures in the past (percutaneous/surgical) [%]	159/0 (23.5/0)	486/10 (22.1/0.5)	NS	
Diabetes mellitus	265 (39.1%)	525 (23.8%)	<0.001	
Arterial hypertension	565 (83.5%)	1499 (68%)	<0.001	
Hypercholesterolaemia	307 (45.3%)	857 (38.9%)	<0.001	
Renal failure	22 (3.25%)	67 (3.0%)	NS	
Peripheral artery disease	107 (15.8%)	359 (16.3%)	NS	
COPD	24 (3.6%)	119 (5.4%)	NS	

Table I. Demographic data and comorbidities with respect to gender

Abbreviations: BMI – body mass index, LVEF – left ventricular ejection fraction, COPD – chronic obstructive pulmonary disease

from the Euroscore (Table II). Operations with the use of cardiopulmonary bypass and on the beating heart were performed at similar rates in both patient groups (Table III). A comparable number of aorto-coronary grafts were implanted as well as arterial anastomoses performed in women and men. Percentage of complete arterial revascularisation was similar in women and men (Table IV).

Statistical analysis

Categorical variables are reported as percentages and continuous variables as means±standard deviation. Mann-Whitney U test was used to compare the quantitative parameters since they did not fulfil the criteria of normal distribution. The qualitative parameters were compared using χ^2 test. Statistical significance was considered at the level of 95% (p <0.05). All statistical analyses were carried out using STATISTICA 6.0 software.

To find parameters with a significant impact on patient mortality following CABG, multivariate analysis was carried out. The analysis of regression involved 14 potential risk factors: age, gender, chronic obstructive pulmonary disease, renal failure, left ventricular ejection fraction (LVEF), BMI, history of MI, use of cardiopulmonary bypass, complete arterial revascularisation, previous PCI, hypertension, hypercholesterolaemia and the presence of peripheral artery atherosclerosis.

Results

Mean cardiopulmonary bypass time in women and men was 86.8 min (19 to 356 min) and 84.7 min (23 to 326 min), respectively (NS). Mean aortic cross-clamping time was 49.6 min in women (19 to 170 min) and 49.5 min (15 to 140 min) in men (NS). **Table II.** Estimation of surgical risk according to the Euroscore calculated for women and men. Evaluation of the risk after elimination of gender input (one point)

Parameter	Women	Men	р
Euroscore	4.2	3.04	<0.001
Euroscore after subtraction of one point for gender	3.2	3.04	NS

Table III. Number of operations depending ontype of surgery and subgroups of patients

Operation method	Total	Women	Men	р
On-pump*	1715 (59.5%)	402 (59.4%)	1313 (59.6%)	NS
Off-pump**	1166 (40.5%)	275 (40.6%)	891 (40.4%)	NS

*with use of extracorporeal circulation ** without use of extracorporeal circulation

 Table IV. Mean number of grafts per patient, including arterial ones

Parameter	Women	Men	р
Number of grafts	2.68	2.73	NS
Number of arterial grafts	1.1	1.1	NS
Complete arterial revascularisation	98 (14.5%)	340 (15.4%)	NS

In the early postoperative period LV failure requiring intra-aortic balloon pumping support and infusion of high doses of catecholamines was more frequent in female patients. Perioperative MI was also detected more often in this patient group. In women, repeat

care unit and of in-hospital stay)			
Parameter	Women	Men	р
Low cardiac output syndrome	149 (22.1%)	354 (16.1%)	<0.001
Dose of epinephrine >0.1 µg/kg/min	38 (5.6%)	70 (3.2%)	< 0.001
Intra-aortic balloon pumping	48 (7.1%)	100 (4.5%)	< 0.001
Perioperative myocardial infarction	37 (5.5%)	64 (2.9%)	< 0.001
Reoperation	60 (8.9%)	112 (5.1%)	<0.001
Necessity of blood transfusion	308 (45.5%)	597 (27.1%)	< 0.001
Acute renal failure	40 (5.9%)	75 (3.4%)	<0.001
Renal replacement therapy	17 (2.5%)	21 (0.95%)	<0.001
Stroke	15 (2.2%)	30 (1.4%)	NS
Mechanical ventilation time (mean) [hours]	16.8	14	< 0.001
Length of postoperative care unit stay (mean) [hours]	42	35	<0.01
Hospitalisation duration (mean) [days]	7.1	6.5	<0.001

Table V. Complications in the early postoperative period and their consequences (period of postoperative care unit and of in-hospital stay)

Table VI. Mortality with respect to type of operation used

Parameter	Women	Men	р
Overall mortality	24 (3.55%)	36 (1.63%)	<0.01
Off-pump* mortality	6 (2.18%)	12 (1.35%)	NS
On-pump** mortality	18 (4.48%)	24 (1.83%)	<0.01

* with use of cardio-pulmonary bypass

** without use of cardio-pulmonary bypass

Table VII. Risk factors of mortality

Factor	OR	-95Cl	+95Cl	р
Age	1.04	1.01	1.08	0.0197
Female gender	2.75	1.55	4.88	0.0005
LVEF	0.97	0.95	1.00	0.0450
BMI	0.92	0.85	0.99	0.0350
Peripheral artery disease	2.08	1.12	3.88	0.0202

Abbreviations: see Table I

operations were performed significantly more often and more females required blood transfusions. Female gender was associated with higher incidence of postoperative acute renal failure. Postoperative stroke rates were similar in both groups. Women required longer mechanical ventilation, and longer stay in the postoperative intensive care unit as well as in the hospital (Table V).

Early mortality in women was 3.6% and was significantly higher than in men (1.6%). Mortality

associated with revascularisation procedures performed off-pump was similar in both groups while in the case of CABG carried out using cardiopulmonary bypass was significantly higher in women (Table VI).

The multivariate analysis showed that age, gender, LVEF, BMI and concomitant peripheral arterial disease had an adverse impact on mortality of patients undergoing CABG surgery (Table VII). Female gender was found to be an independent risk factor of death among patients operated on for CAD.

Discussion

The real problem in comparing the results of CABG surgery in women and in men is their heterogeneity in terms of baseline characteristics. Risk factors of the operative mortality are common in women. Abramov et al. documented that the difference in risk factor profile between women and men had a more pronounced impact on the results of treatment than female gender itself [10]. However, female gender is still considered an independent risk factor when performing CABG surgery.

In the patient group analysed herein, the operative risk was calculated according to the Euroscore, which assumes one point for female gender. After subtracting this one point, estimated predicted operative risk in women and men was similar, but in reality mortality in women was found to be two times higher than in men. Female gender itself seems to be protective with respect to the late results of CABG [2].

The studies that involved large numbers of patients revealed that the internal mammary artery as well as the radial artery were used less frequently and fewer aorto-coronary grafts were implanted in women [2]. The analysis performed in our study did not confirm such a trend. It should be emphasised that in a comparable percentage of women and men complete arterial revascularisation was performed.

Hypercholesterolaemia and atherosclerosis also affect microcirculation. This phenomenon involves both small arterioles and resistance vessels of the coronary microvasculature [11]. Impaired endothelial relaxation, increased number of adrenoreceptors and serotoninergic receptors, and hypersensitivity of the smooth muscle cell for calcium ions are responsible for abnormal microcirculation reactivity. Pathological microcirculation reactivity is associated with endothelium-derived relaxing factor (EDRF) depletion or release impairment. Atherosclerotic lesions in women are seen more frequently within microcirculatory vessels. Their dysfunction, more common in women, may have an impact on abnormal intraoperative myocardial protection caused by impaired cardioplegic solution penetration. The attempts to normalise the reactions of microcirculation include administration of L-arginine together with cardioplegic solution infused to the coronary arteries [11].

A study performed on a large number of healthy women in postmenopausal age documented that elevated C-reactive protein (CRP) and interleukin-6 (IL-6) concentrations were independent risk factors of CAD [12]. Long-term hormone replacement therapy is associated with further increase of CRP level. It has been established that elevated CRP level is an independent risk factor of CAD in healthy and elderly women [13, 14]. Moreover, leukocytosis exceeding 6.7 × 10⁹/l was shown to be associated with cardiac events and mortality in older women [15]. Low grade inflammatory reaction is seen more often in the overweight and obese individuals. It is estimated that 25% of IL-6 is released from subcutaneous adipose tissue. Interleukin stimulates production of acute phase protein in the liver. Women have more adipose tissue deposits than men, so overweight and obese women present higher CRP concentrations than men of similar parameters with regards to BMI [16]. Extracorporeal circulation induces cytokine release. Concentration of pro-inflammatory cytokines such as interleukin-6 and interleukin-8 is positively correlated with cardiopulmonary bypass duration [17].

The technical aspects of CABG in women (small vessel diameter) may also contribute to a prolonged time of extracorporeal perfusion. In women with higher blood CRP concentration, a systemic inflammatory response may be provoked much more easily. Its clinical manifestation may have a very mild course with discrete symptoms of trivial organ dysfunction, but may also present as severe multiorgan failure. So far no efficacious methods of either prevention or treatment of systemic

inflammatory response have been developed [18]. One may consider administration of steroids immediately before starting extracorporeal circulation. These agents limit severity of ischaemic-reperfusion injury and inhibit inflammatory response to the extracorporeal circulation. Another attempted agent is aprotinin, an antioxidant agent that may play a key role in the inhibition of inflammation activation and which additionally is known to decrease postoperative drainage and improve fluid balance, lung function and right ventricular performance [17]. Removal of the circulating inflammatory mediators is facilitated by the use of ultrafiltration during the extracorporeal circulation. Statins reduce plasma CRP concentration [19]. Chronic statin therapy in the period preceding the operation would be able to limit the severity of the inflammatory response following cardiopulmonary bypass.

Diastolic myocardial dysfunction is more frequently seen in elderly people, especially those suffering from hypertension, diabetes mellitus and CAD [20]. This form of heart failure often affects women and is related to heterogeneous, gender-dependent response of myocardium to ischaemic injury and less common use of angiotensin-converting enzyme inhibitors and betablockers in women. Diastolic dysfunction is less frequently accompanied by decreased LVEF (<50%) in women than in men. In the preoperative evaluation of risk factors (according to the Euroscore) such form of myocardial dysfunction is not taken into account, but it may have an impact on the onset of low cardiac output syndrome in the early postoperative period. Analysis of pharmacotherapy used prior to surgery in our patients revealed that the prescription rate of beta-blockers and ACE inhibitors was similar in both examined groups.

Conclusions

Among CABG patients analysed in our study women were older, and more frequently had diabetes mellitus and hypertension that might lead to diastolic heart failure. The operative aspects (such as smaller vessel diameter and diffuse atherosclerotic lesions) may contribute to incomplete intraoperative myocardial protection during the aortic clamp period. The main cause of more than two times higher mortality in women than in men was higher incidence of postoperative low cardiac output syndrome followed by multiorgan dysfunction. Contributing to the development of low cardiac output syndrome may be: 1) preoperative, diastolic heart failure, 2) systemic inflammatory response induced by extracorporeal perfusion, 3) insufficient myocardial protection, and 4) early occlusion of coronary grafts caused by distal CAD. In order to limit heart failure occurrence in the early postoperative period and to diminish the symptoms of systemic inflammatory reaction, perioperative prevention should focus on optimal myocardial protection. One may also consider wider use of hybrid procedures, i.e. CABG accompanied by subsequent percutaneous interventions on coronary vessels not amenable to surgical revascularisation.

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Wczesne wyniki chirurgicznej rewaskularyzacji tętnic wieńcowych u kobiet

Bronisław Czech¹, Ewa Kucewicz-Czech², Jerzy Pacholewicz¹, Jacek Wojarski¹, Jacek Puzio², Roman Przybylski¹, Arkadiusz Farmas¹, Bogdan Ryfiński¹, Marian Zembala¹

¹ Katedra i Oddział Kliniczny Kardiochirurgii i Transplantologii, Śląska Akademia Medyczna, Śląskie Centrum Chorób Serca, Zabrze
² Oddział Kliniczny Kardioanestezji i Intensywnej Terapii Pooperacyjnej, Śląska Akademia Medyczna, Śląskie Centrum Chorób Serca, Zabrze

Streszczenie

Wstęp: Choroba wieńcowa jest jedną z głównych przyczyn zgonów kobiet w populacji rozwiniętych społeczeństw całego świata. Chirurgiczna rewaskularyzacja mięśnia sercowego jest udokumentowaną metodą leczenia rozsianej miażdżycy tętnic wieńcowych.

Cel: Retrospektywna ocena wczesnych wyników chirurgicznej rewaskularyzacji tętnic wieńcowych u kobiet i ich odniesienie do wyników uzyskanych w grupie mężczyzn.

Metodyka: Analizą objęto 2881 chorych (677 kobiet, 2204 mężczyzn), którzy w latach 2003–2005 zostali poddani operacji pomostowania tętnic wieńcowych. Czas obserwacji dotyczył okresu hospitalizacji związanej z operacją. Z badania wykluczono pacjentów, u których wykonano dodatkowe procedury medyczne (plastyki czy wymiany zastawek serca, korekcje wad wrodzonych, tętniaki aorty wstępującej itd.). W grupie kobiet i mężczyzn z porównywalną częstością wykonywano zabiegi w trybie planowym, pilnym i ze wskazań życiowych. Kobiety charakteryzowało wyższe ryzyko operacyjne wyliczone wg skali Euroscore (4,2 vs 3,04, p <0,001). Z użyciem krążenia pozaustrojowego wykonano 1715 operacji (59,5%), techniką off pump przeprowadzono 1166 procedur (40,5%); 402 zabiegi (23,4%) z wykorzystaniem perfuzji pozaustrojowej wykonano u kobiet, pozostałe 1313 (76,6%) przeprowadzono u mężczyzn. W grupie operacji małoinwazyjnych 23,6% (275) stanowiły operacje wykonane u kobiet, 76,4% (891) – u mężczyzn. Operacje z użyciem i bez użycia krążenia pozaustrojowego były przeprowadzane z porównywalną częstością w obu grupach. W analizowanej grupie chorych kobiety były starsze niż mężczyźni, charakteryzowały się wyższym wskaźnikiem masy ciała (BMI) i lepszą funkcją lewej komory serca. Dodatkowymi schorzeniami częściej występującymi u kobiet były cukrzyca, nadciśnienie tętnicze i hipercholesterolemia. Obciążenie niewydolnością nerek, miażdżycą tętnic obwodowych i przewlekłą obturacyjną chorobą płuc było porównywalne w obu grupach. Przebyty zawał lub zawały serca znamiennie częściej stwierdzano w grupie mężczyzn. Dwa i więcej przebytych zawałów miało 13,5% kobiet i 20,5% mężczyzn zakwalifikowanych do operacji. Przezskórne i chirurgiczne zabiegi rewaskularyzacji serca wykonane w przeszłości odnotowano w obu grupach z taką samą częstością. U kobiet i mężczyzn wykonywano porównywalną liczbę pomostów, w tym także zespoleń tętniczych. Pełną rewaskularyzację tętniczą wykonywano z taką samą częstością u kobiet i mężczyzn.

Wyniki: Średni czas krążenia pozaustrojowego w grupie kobiet wynosił 86,8 min (19–356), w grupie mężczyzn 84,7 min (23–326) (NS). Średni czas zaklemowania aorty w grupie kobiet wynosił 49,6 min (19–170), w grupie mężczyzn 49,5 min (15–140) (NS). W okresie pooperacyjnym u kobiet częściej niż u mężczyzn rozpoznawano niewydolność lewej komory serca wymagającą zastosowania kontrapulsacji wewnątrzaortalnej i dużych dawek amin katecholowych (odpowiednio 22,1% i 16,1%; p <0,001). Z wyższą częstością diagnozowano w grupie kobiet okołooperacyjny zawał serca (5,5 vs 2,0%, p <0,001). U pacjentek znamiennie częściej wykonywano reoperacje (8,9 vs 5,1%, p <0,001) i wymagały one częściej przetaczania krwi (45,5 vs 27,1%, p <0,001). Płeć żeńską charakteryzowało częstsze występowanie pooperacyjnej ostrej niewydolności nerek (5,9 vs 3,4%, p <0,001). Udar ośrodkowego układu nerwowego wikłał przebieg pooperacyjny porównywalnie często w obu grupach. U kobiet dłużej stosowano wentylację mechaniczną płuc, wymagały one dłuższego pobytu na oddziale pooperacyjnym i dłuższej hospitalizacji. Wczesna śmiertelność kobiet wyniosła 3,6% i była znamiennie wyższa niż mężczyzn (1,6%) (p <0,01). Śmiertelność w operacjach rewaskularyzacji wykonanych metodą *off pump* była w obu grupach porównywalna i wyniosła dla kobiet 2,2%, a dla mężczyzn 1,4%. W operacjach z użyciem krążenia pozaustrojowego śmiertelność kobiet była znamiennie wyższa niż mężczyzn (4,48 vs 1,83%) (p <0,01).

Wnioski: Wykonana analiza wskazuje na wyższą śmiertelność kobiet, w stosunku do mężczyzn, po zabiegach rewaskularyzacji tętnic wieńcowych.

Słowa kluczowe: choroba niedokrwienna serca, pomostowanie tętnic wieńcowych, kobiety, powikłania, śmiertelność

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Adres do korespondencji:

dr hab. n. med. Ewa Kucewicz-Czech, Oddział Kliniczny Kardioanestezji i Intensywnej Terapii Pooperacyjnej, ŚlAM, Śląskie Centrum Chorób Serca, ul. Szpitalna 2, 41-800 Zabrze, tel./faks: +48 32 273 27 31, e-mail: kardanest@slam.katowice.pl **Praca wpłynęła:** 20.09.2006. **Zaakceptowana do druku:** 21.02.2007.