Outcome in cardiac surgery

Outcome in cardiac surgery: differences between men and women

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Uitkomsten van hartchirurgie: verschillen tussen mannen en vrouwen

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Voor Bettina,
In nagedachtenis aan mijn vader,
Voor mijn patienten

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CHAPTER 1

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Introduction

General Introduction

Cardiovascular disease (CVD) is traditionally seen as a men's disease but nowadays it is the leading cause of mortality for women both in the United States and globally [1]. In Europe, deaths due to CVD are higher in women than in men (49% versus 40%). However, fewer women than men under the age of 65 died from CVD, as the main cause of death in women is malignancy [2]. Men and women undergoing coronary bypass grafting (CABG) have a different preoperative patient profile. It has been reported that women have more perioperative co-morbidities and less favorable postoperative outcomes [3].

In developed countries, aortic valve stenosis (AoS) is the most common heart valve disease in the elderly (>75 years old) in whom the prevalence for severe AoS is 3.4% [4]. In case of isolated aortic valve replacement (AVR), predictive models to estimate perioperative mortality such as the EuroSCORE and the STS score, include female sex as one of the risk factors for unfavorable outcomes [5,6]. Transfusion of blood products is a common practice after CABG and AVR. Earlier reports have demonstrated increased short-term and long-term morbidity and mortality after blood product transfusion [7]. Differences between the two sexes concerning transfusion practices needs to be investigated.

Coronary artery disease

The efficacy of CABG for the treatment of coronary artery disease (CAD) has been demonstrated in multiple prospective, randomized studies [8]. Risk factors among patients with CAD undergoing CABG have been intensely investigated and sex-specific recommendations have improved hospital practice [9]. Women are at higher risk for morbidity and mortality in most studies and they have more risk factors as hypertension, diabetes, heart failure, chronic respiratory disease and peripheral vascular disease [10].

Women are older when they present themselves with symptoms of CAD despite the fact that women have more risk factors [11]. This delayed manifestation of atherosclerotic disease in females is believed to be the result from exposure to endogenous estrogen in their premenopausal period [12]. Estrogen restricts atherosclerotic development and delays the presentation of symptomatic CAD in females. After the menopause, estrogen levels decrease significantly and the process of atherosclerosis process worsens. There is some evidence that off-pump coronary artery bypass operation (OPCAB) shows a beneficial effect for women compared to on-pump coronary artery bypass grafting (CABG) [13]. This effect might be due to the avoidance of the extra-corporeal circulation (ECC), which can lead to an inflammatory response caused by activated polymorphonuclear leucocytes [14]. Another factor which could contribute to a beneficial effect of the OPCAB surgery could be a higher postoperative hemoglobin level in OPCAB patients compared to on-pump CABG patients [15].

Aortic valve disease

The most common valvular heart disease in developed countries is aortic stenosis (AoS), and it is still increasing due to the aging of the Western populations [16]. Because there are no effective medical therapies for AS, management relies on optimal timing of surgical aortic valve replacement (SAVR), resulting in improvement in left ventricular hypertrophy (LVH), systolic and diastolic ventricular function, symptoms, and survival [17]. Given the poor natural history of untreated symptomatic AS, any symptomatic patient with severe AS should be considered for AVR [18]. Surgical AVR is associated with an operative mortality of 1%–3% in patients aged < 70 years, and 3%–5% in older patients [5,6]. Compared to men, women are older at time of surgery and have higher rates of hypertension, diabetes mellitus, chronic obstructive lung disease, and anemia. In-hospital mortality is assumed to be higher in women than in men; this is probably due to the fact that women have more co-morbidities at time of presentation. Since transcatheter aortic valve implementation (TAVI) became commercially available in the United States and Europe, women have been referred more often to TAVI instead of SAVR compared with men [19].

Risk factors

In general, women have more risk factors than men at the time of surgery. They are older at presentation, have more often hypertension, diabetes, peripheral vascular disease (PVD), lower hematocrit and chronic obstructive pulmonary disease (COPD) [9,20]. Female sex is an independent predictor of morbidity and mortality after cardiac surgery, it is included in risk stratification scores like the EuroSCORE and the STS score [5,6,21]. Surgical outcome is possibly associated with parameters specific to female sex: smaller coronary artery size and fewer bypass grafts [20]. Women often present with a lower preoperative hematocrit, compared to men; this is also associated with unfavorable outcome after cardiac surgery [22]. Female sex is still an independent predictor of increased mortality after cardiac surgery, after adjustment for the well-known risk factors as mentioned above [21]. Women are older at presentation for cardiac surgery, mostly post-menopausal. Advanced age is associated with diabetes, hypercholesterolemia, hypertension and cerebrovascular disease. These factors may accelerate the progress of CAD and could lead to more severe CAD, compared to men [23]. In case of isolated aortic valve replacement (AVR), women have distinctive risk profiles compared to men, and results are more controversial [24-26]. In the EuroSCORE or the STS score female sex is one of the risk factors for unfavorable outcome after AVR, although these models were originally based on CABG populations [27]. Finally, the transfusion of blood is known to be associated with increased short-term and long-term morbidity and mortality after CABG and female sex remains one of the risk factors of receiving a perioperative blood transfusion after cardiac surgery [28-30].

Objectives in this thesis

The aim of this thesis was to evaluate the morbidity and mortality outcomes in our patient population for cardiac surgery, and to identify the differences in outcome between the two sexes. When we can identify specific risk factors for women compared to men, a careful decision-making process could improve the outcome of cardiac surgery especially for women.

The following questions were posed:

1. What are the differences between the sexes in coronary artery bypass grafting concerning preoperative profile and early outcome (chapter 2), as well as long-term outcome (chapter 3)?
2. Is off pump coronary artery bypass grafting more beneficial for women compared to men (chapter 4)?
3. What is the impact of sex on the outcome of isolated aortic valve replacement (chapter 5)?
4. What is the role of sex on blood transfusion in coronary artery bypass grafting (chapter 6)?

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CHAPTER 2

2

Sex difference in coronary artery bypass grafting: preoperative profile and early outcome

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Objective: According to the available risk stratification systems, women have a higher risk of mortality than men after coronary artery bypass grafting. In this study, we investigated our coronary artery bypass grafting database to trace factors contributing to this difference in outcome between sexes.

Design: A retrospective patient record study.

Setting: This single-center study was performed at the Catharina Hospital in Eindhoven, the Netherlands.

Participants: The study comprised 17,919 patients, of whom 4,016 (22.4%) were women and 13,903 (77.6%) were men.

Interventions: Coronary artery bypass grafting was performed between January 1998 and July 2016.

Measurements and Main results: Early mortality was significantly higher in women than in men (2.7% vs. 1.9%; p=0.001). Regarding the baseline characteristics, women were older and had a lower hemoglobin level and a lower creatinine level than men. Women had more often hypertension, diabetes, underweight (BMI <20 Kg/m2) and obesity (BMI >30 Kg/ m2). The mean number of grafts per patient was less in women than in men (3.2 ±1.1 vs. 3.5 ±1.1; p<0.001). However, the mean x-clamp time per graft was longer in female than in male patients (11.6 ±8.7 min. vs. 11.2 ±7.0 min.; p=0.013). Logistic regression analyses showed that chronic obstructive pulmonary disease, peripheral vascular disease, x-clamp time and underweight were independent risk factors for early mortality only in men.

Conclusions: The preoperative patient profile is significantly different between our men and women undergoing coronary artery bypass grafting. The predictive value of well-known risk factors for early mortality is different between the two sexes.
Keywords: coronary artery bypass grafting; sex; early mortality

Female gender is an important risk factor for morbidity and mortality after coronary artery bypass grafting (CABG) [1]. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) [2] has been considered the predictive model of choice in Europe to estimate early mortality after cardiac surgery. In North America, however, the Society of Thoracic Surgeons (STS) score is preferred [3] According to the EuroSCORE, female gender predicts higher mortality. However, other risk factors included in the model weigh equally in both sexes [2]. Earlier reports [4] found that the EuroSCORE more accurately predicted mortality among female patients compared to the STS risk score. Despite the decrease in overall operative mortality in patients undergoing CABG over the previous decade, the higher risk of female gender has persisted [5-8]. Because women represent a growing population of patients undergoing cardiac surgery, it is important to understand the factors contributing to the higher mortality in the female population after CABG [5]. Women seem to be older when operated for coronary artery disease (CAD) compared to men [9] and have more often hypertension, diabetes, and a higher need for blood transfusion [10-13]. There is a growing need to understand the risk factors associated with operative mortality in woman undergoing CABG. For this reason, we investigated the data of mortality and sex in patients who underwent isolated CABG in our institution since 1998.

Methods

Patients

In this study, we analyzed the data of all patients undergoing isolated CABG with or without the use of extra-corporal circulation (ECC) in a single center (the Catharina Hospital, Eindhoven, the Netherlands) between January 1998 and July 2016. Clinical data, including demographic information, risk factors, complications and survival were prospectively collected in the computerized database of the Department of Cardiothoracic Surgery. Preoperative baseline characteristics included in the analysis were: age, underweight (Body Mass Index (BMI), hypertension, chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), diabetes mellitus, left ventricular ejection fraction (LVEF) < 35%, hemoglobin, and triple vessel disease. Underweight was defined as a body mass index (BMI) of ≤20 Kg/m2 and obesity as a BMI of >30 Kg/m2. Emergency operations included cases that are discussed in the heart team and performed before the following working day because of instable hemodynamics. Concerning the intraoperative data, the cross-clamp time/graft was calculated retrospectively for every patient. The mean of the whole population was then calculated. The medical ethical committee of the hospital approved the study and waived the need for an informed consent. The primary end point of the study is early mortality, defined as death occurring within 30 days after the operation.

Operative techniques

All patients received short-acting anesthesia to facilitate rapid extubation. In CABG the ECC was normothermic with a non-pulsatile flow. Cardioplegic arrest was accomplished by the use of cold crystalloid cardioplegia (St Thomas' solution) or warm blood cardioplegia, according to the surgeon's preference.

Statistical analyses

Discrete variables were compared using the Chi-square test and are presented as percentages. Continuous variables were compared with a unpaired T-test, when normal distributed and are presented as means ± standard deviation. Continuous variables were compared with a Mann Whitney test, in case of not normally distributed and were presented as median (25-75% interquartile range). Univariable and multivariable logistic regression analyses were performed to investigate the association of several preoperative and perioperative factors with early mortality. Patients were excluded from the LR analysis if one of the variables was missing. Two different regression models were performed: one for each sex. Univariable analyses were used to test the potential correlation of biomedical and demographic factors with outcome. If significant at p <0.05, baseline variables were included into the multivariable logistic regression model. A p-value <0.05 was used to all tests to indicate statistical significance. Odds ratio (OR) with 95% confidence intervals (CI) are reported. All statistical analyses were performed using IBM SPSS Statistics 23.0 (SPSS Inc., Chicago, IL).

Results

During an eighteen-year-period (January 1998 till July 2016), 17 919 patients underwent isolated CABG in our hospital. Demographic data of the patients are shown in table 1. There were 4016 women (22.4%) and 13903 (77.6%) men. Women had more often hypertension, diabetes, underweight (BMI <20 Kg/m2) and obesity (BMI >30 Kg/ m2). Female patients were older at the time of operation, had a lower hemoglobin level and a lower creatinine level. Table 2 shows the difference between male and female patients regarding relevant perioperative data. The mean number of grafts per patient is significantly less in women than in men. Consequently, both the x-clamp time and ECC duration are shorter in women than in men. However, the mean x-clamp time needed to perform one graft is longer in women than in men. As shown in table 3, the incidence of early mortality is significantly higher in women than in men (2.7% vs. 1.9%; p=0.001). The incidence of postoperative CVA was also higher in women (1.2%) than in men (0.6%); p<0.001. Univariate analysis of the two groups (table 4) shows differences in the predictive value of perioperative risk factors. Chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), X-clamp time, underweight and preoperative atrial fibrillation (AF) were only in men. Cerebral vascular accident (CVA), prior cardiac surgery, hemoglobin level, creatinine level, age and

Table 1. Preoperative and demographic characteristics

Variable	Women n=4,016	Men n=13,903	p-value
Age, year, mean	68.2 ±9.6	64.4 ±9.8	<0.001
Hypertension	2,306 (57.4%)	6,216 (44.7%)	<0.001
COPD	463 (11.5%)	1,504 (10.8%)	0.207
PVD	506 (12.6%)	1,727 (12.4%)	0.767
Prior CVA	181 (4.5%)	592 (4.3%)	0.510
Reoperation	181 (4.5%)	725 (5.2%)	0.073
Underweight	132 (3.3%)	161 (1.2%)	<0.001
Obesity	307 (7.6%)	497 (3.6%)	<0.001
Diabetes	1,124 (28.0%)	2,765 (19.9%)	<0.001
- Insulin-dependent	385 (9.6%)	816 (5.9%)	
- Non-insulin-dependent	621 (15.5%)	1,581 (11.4%)	
- Diet-controlled	117 (2.9%)	366 (2.6%)	
Emergency	109 (2.7%)	202 (1.5%)	<0.001
LVEF<35%	122 (3.0%)	504 (3.6%)	0.081
Hemoglobin level, mmol/L, mean	7,9 ± 1,1	8,8 ± 1,1	0.004
Creatinine level, µmol/L, mean	89.7 ±39.8	101.5 ±39.4	<0.001
Preoperative AF	121 (3.0%)	413 (3.0%)	0.878
3-vessel disease including main stem stenosis	2,305 (57.4%)	8,661 (62.3%)	0.085

Categorical variables are presented as percentage; continuous variables as mean ± standard deviation. AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; PVD, peripheral vascular disease.

Table 2. Operative data

Variable	Women n=4,016	Men n=13,903	p-value
Duration of CPB, min*	57.2 (±35.1)	59 (±35.5)	<0.001
Aortic cross-clamp time, min*	37.6 (±24.2)	40 (±23.7)	<0.001
ICU stay, days**	1.0 (1-56)	1.0 (1-95)	<0.001
Hospital stay, days**	7.0 (2-127)	7.0 (2-153)	0.728
Number of grafts*	3.2 (±1.1)	3.5 (±1.1)	<0.001
Aortic cross-clamp time/graft, min*	11.6 (±8.7)	11.2 (±7.0)	0.013

Data are presented as *mean ± SD or **median (range). CPB, cardiopulmonary bypass; ICU, intensive care unit

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LVEF<35% were significant predictors of early mortality in both groups, whereas diabetes was significant only in women. All perioperative risk factors identified with univariate analyses were entered into the multivariable logistic regression model (table 5). This analysis shows considerable differences between the two sexes: COPD, PVD, X-clamp time and underweight were identified as independent risk factors for early mortality only in men. For both sexes, prior cardiac surgery, hemoglobin level, creatinine level, age and LVEF<35% were identified as independent risk factors for early mortality. However, CVA, preoperative AF and diabetes were not identified as independent risk factors for early mortality. Figure 1 shows the predictive probability of early mortality according to hemoglobin level of both sexes, a lower preoperative hemoglobin level is an independent predictor of early mortality, equally in both men and women. Figure 2 shows the predictive probability of early mortality according to creatinine level of both sexes. A higher creatinine level is independent predictor of early mortality but the weight of the creatinine level is not the same for either sexes.

Table 3. Postoperative complications and early mortality in both groups

Variable	Women n=4,016	Men n=13,903	p-value
Mediastinitis	36 (0.9%)	128 (0.9%)	0.993
Re-exploration	192 (4.8%)	793 (5.7%)	0.026
Perioperative infarction	131 (3.3%)	380 (2.7%)	0.083
Postoperative CVA	43 (1.2%)	85 (0.6%)	<0.001
Postoperative new-onset AF	652 (16.2%)	2,358 (17.0%)	0.292
Early mortality	110 (2.7%)	259 (1.9%)	0.001

Variables are presented as number (%). AF, atrial fibrillation; CVA, cerebrovascular accident

Discussion

The main finding of the present study is the considerable difference in preoperative patient profile between male and female populations undergoing CABG in our institution. In agreement with earlier studies, women were older than men at the time of CABG and had greater number of preoperative co-morbidities including hypertension, diabetes, obesity, and anemia [1]. In addition, the weight of individual risk factors in predicting early mortality is not equal in either populations. Our study showed that women are operated at a relatively older age than men. Other studies have implicated coronary microvascular disease in women, which may account for greater disabling symptoms [14] despite less extensive coronary artery disease [15] and more preserved LV ejection fraction. It is likely that women experience a delayed onset of cardiac disease, compared with men, until the onset of menopause, presumably because of the protective effects of estrogen on the cardiovascular system [16]. Estrogen plays a complex role in CAD formation and myocardial infarction risk. Exogenous estrogen in postmenopausal women has not demonstrated cardioprotective effects and may be associated with increased thrombotic complications [17,18]. It is also possible that women are more likely to present late for surgery as evidenced by the larger proportion of urgent and emergency acuity patients [6]. Our study showed a higher incidence of emergency operations in women than in men; a finding that could attribute to the worse outcome in female patients. This is consistent with a report that women have a fear of surgery [19], which might result in delayed referral for CABG. Older age at the time of the operation couldn't solely explain the higher early mortality in women. Even after correcting the results according to age, women still have a higher risk of mortality [2]. Interestingly, an earlier report [6] found that younger women, defined as those ≤ 65 years old, had the highest likelihood of death compared to men. In addition, Hogue et al [7] have demonstrated a higher incidence of postoperative stroke in women compared to men.

Table 4. Univariate logistic regression analyses for predictors of early mortality stratified by sex

Variable	Women		Men	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, year	1.059 (1.033-1.086)	<0.0001	1.083 (1.067-1.100)	<0.001
Hypertension	1.073 (0.730-1.578)	0.719	0.787 (0.612-1.013)	0.063
COPD	1.522 (0.909-2.546)	0.11	2.162 (1.591-2.938)	<0.001
Diabetes	1.612 (1.090-2.383)	0.017	1.302 (0.977-1.734)	0.072
LVEF<35%	5.128 (2.836-9.274)	<0.0001	6.040 (4.323-8.441)	<0.001
PVD	1.098 (0.632-1.909)	0.74	2.215 (1.655-2.965)	<0.001
CVA	2.184 (1.12-4.259)	0.022	2.020 (1.283-3.181)	0.002
Prior cardiac surgery	4.171 (2.430-7.158)	<0.0001	5.350 (3.940-7.265)	<0.001
Preop. Hemoglobin, mmol/L	0.595 (0.465-0.761)	<0.0001	0.592 (0.513-0.684)	<0.001
Serum Creatinine, μmol/L	1.004 (1.002-1.006)	<0.0001	1.005 (1.004-1.006)	<0.001
Underweight	1.731 (0.746-4.016)	0.202	3.589 (1.869-6.889)	<0.001
Obesity	1.215 (0.628-2.353)	0.563	0.857 (0.422-1.743)	0.671
Preoperative AF	1.902 (0.818-4.421)	0.135	2.350 (1.423-3.882)	0.001
X-clamp time, min	1.006 (1.000-1.012)	0.069	1.005 (1.000-1.010)	0.049
Number of grafts	1.016 (0.853-1.210)	0.857	0.908 (0.812-1.016)	0.093

AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; PVD, peripheral vascular disease

They concluded that the relatively worse outcome in women after CABG might be attributed to increased risk of CVA. Our results are in agreement with their conclusions as the incidence of postoperative CVA in our female population is as twice as that in the male population. However, our data didn't show the nature (hemorrhagic/ embolic) or the severity (limited/

Table 5. Multivariable logistic regression analysis for predictors of early mortality stratified by sex

Variable	Women		Men	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.056 (1.029-1.084)	<0.0001	1.068 (1.050-1.086)	<0.001
Diabetes	1.433 (0.958-2.143)	0.08		
LVEF<35%	4.830 (2.610-8.937)	<0.0001	4.950 (3.490-7.021)	<0.001
COPD			1.705 (1.241-2.340)	0.001
PVD			1.529 (1.128-2.074)	0.006
Prior CVA	1.978 (0.993-3.941)	0.52	1.425 (0.891-2.280)	0.139
Prior cardiac surgery	4.733 (2.704-8.285)	<0.0001	4.747 (3.452-6.525)	<0.001
Preop. Hemoglobin, mmol/L	0.736 (0.568-0.954)	0.021	0.797 (0.685-0.927)	0.003
Serum Creatinine, µmol/L	1.004 (1.001-1.006)	0.008	1.004 (1.002-1.005)	<0.001
Underweight			2.878 (1.448-5,721)	0.003
Preoperative AF			1.404 (0.834-2.363)	0.202
X-clamp time, min			1.006 (1.002-1.011)	0.007

AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident;

massive/fatal) of the CVA to correlate it with the poorer prognosis. A large number of studies have shown that estrogen limits the extent of neuronal injury in a variety of in vitro and in vivo experimental models [20,21]. Whether estrogen replacement therapy results in a reduction in perioperative strokes, and consequently early mortality, is not known [7]. It is possible that the technical element of surgery plays an important role in the difference in outcome between male and female patients. It has been earlier reported that women have smaller and thinner coronary arteries than men [20,21]. Surgical grafting to smaller targets can be technically more challenging and impact graft patency and clinical outcomes [22]. According to Swaminathan et al [1], men had a higher rate of triple or quadruple bypass graft utilization compared with women who were more likely to have only 1 or 2 grafts. Overall, the IMA was used less frequently in women [1]. Bukapatnam [6] also found that women were significantly less likely to receive internal mammary artery grafts. In the present study, we found that both the cross-clamp time and the duration of ECC are shorter in women than in men. This could be clarified by the fact that the mean number of grafts performed was less in women than in men. However, the mean cross-clamp time per graft is longer in women than in men. This is in agreement with the findings of earlier studies that CABG in women is more challenging as they have smaller and thinner coronary arteries than men [23]. It is possible that the quality and the caliber of the target vessels limit the number of grafts performed in women. For the same reason, surgeons need longer X-clamp time to perform the anastomoses in women. One of the risk factors associated with poor quality

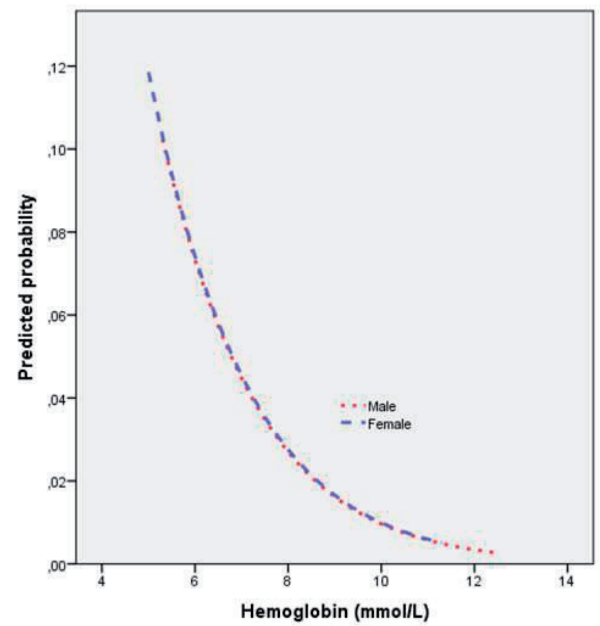

Figure 1. Predictive probability of early mortality in both sexes according to preoperative Hemoglobin level

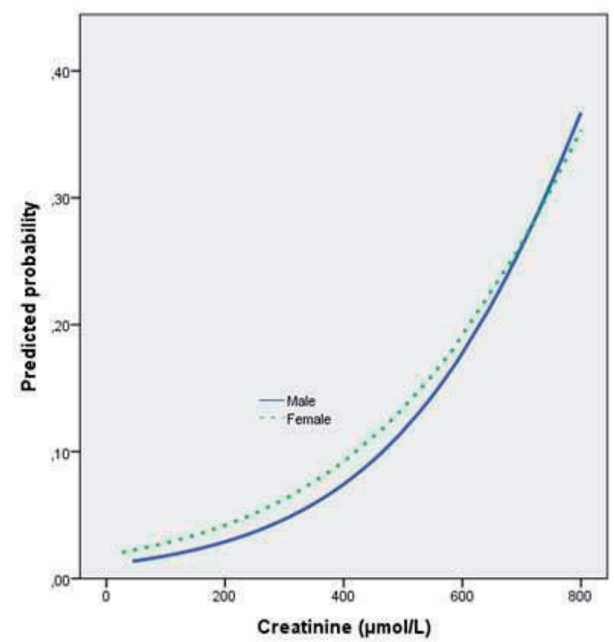

Figure 2. Predictive probability of early mortality in both sexes according to preoperative Creatinine level

of coronary arteries is diabetes. In our study, diabetes is more common in women than in men. However, diabetes was not retrieved as an independent predictor of early mortality in either sexes. In an earlier study [24], we have found that only type 2 diabetes is a significant predictor of early mortality after CABG. In the present study, we didn't divide diabetic patients into type 1 and 2 for the analysis. Another factor that might clarify our present results is our practice of an adequate peri-operative blood glucose monitoring. Blood glucose is regularly measured and corrected intraoperatively so that it could be kept below the level of 10.0 mmol/L (180 mg/dL). Our present population shows a higher incidence of weight disorders (underweight or obesity) in women than in men. This is in consistence with the distribution of weight disorders in the Dutch general population [25]. However, only underweight was retrieved as a significant predictor of early mortality in men and not in women. The effect of hormonal factors and undetected underlying diseases causing underweight could be different between the two sexes. Underlying diseases cannot be always recognized and treated before undergoing CABG. As we earlier reported [26], underweight patients experience relatively increased hemodilution caused by the priming volume of the heart-lung machine. This may exacerbate cardiopulmonary bypass–related coagulopathy, leading to increased postoperative bleeding. This leads in turn to higher morbidity including re-exploration, sternal wound infection apart from complications of blood transfusion often associated with these complications [26]. The preoperative hemoglobin level is lower in women compared to men; the etiology is multifactorial and genetic, environmental and hormonal factors have important roles. Anemia has been identified as a predictor of poor outcome in early and late survival in patients undergoing CABG [27]. The effects of anemia, when not adequately compensated, can lead to tissue hypoxia, cellular failure and eventual organ failure. This difference in hemoglobin level between the two sexes cannot solely explain the difference in early mortality. The predictive probability of early mortality according to hemoglobin level is the same for women as for men. The last important preoperative factor is the preoperative creatinine level which is significantly higher in men than in women. Earlier studies preoperative renal impairment is a well-established predictor of adverse outcome in patients undergoing CABG [27,28]. In agreement with these studies, the present study shows that preoperative serum creatinine is an independent predictor of early mortality in both sexes. Preoperative creatinine levels are higher in men than in women, a finding that is related to the muscle mass which is larger in men than in women. Calculation of the eGFR, as a measure of renal function, is modified for sex. For this reason, at the same level of serum creatinine, predicted probability of early mortality is higher in women than in men as the renal function is worse. The present study has some limitations. This is a retrospective observational single-center study, which may limit generalizability of the results. Some other factors could have confounded our conclusions. Examples of these confounders are preoperative medications, use of arterial grafts, and the operating surgeon. Moreover, possible effects of changes in patient populations and management protocols during the inclusion time can't be excluded. Although medication policy was the same for both sexes, we cannot exclude possible different confounding effect in either sexes. The primary end point was all-cause early mortality. We were not able to retrieve the cause of death which might be equally important. However, death within 30 days postoperatively is mostly a consequence of surgery. The present analysis of more than 17,000 patients undergoing isolated CABG raised important issues. First, apart from age at the time of the operation, differences in many other risk factors have been encountered. Second, the predictive value of known preoperative risk factors for early mortality after CABG varies between men and women. Considering female sex as *merely* one of the risk factors might be revised. This is also confirmed by the observation that the preoperative patient profile considerably differs between the two sexes. Strikingly, multivariate regression analyses of the female population showed that COPD, PVD, CVA, pre-operative AF and diabetes are no significant predictors for early mortality, in contrast to the finding of other studies [29] On the other hand, COPD, PVD, X-clamp time and underweight are retrieved as independent risk factors for mortality in our male patients, as also shown by other studies [30]. The well-known and worldwide used risk stratification scores including the EuroSCORE [2] or the Society of Thoracic Surgeons (STS) score [3] use the patient related factor 'sex', all other factors are equally weighed for men and women. In developing future risk scoring systems, more attention is needed for sex-specific risk factors.

Conclusion

In our large CABG database, the preoperative patient profile is significantly different between men and women. Women were older and had a lower hemoglobin level and a lower creatinine level than men. Women had more often hypertension, diabetes, underweight and obesity. The incidence of early mortality is significantly higher in women than in men. However, the predictive value of well-known risk factors for early mortality is different between the two sexes. For instance, COPD, PVD, and underweight were identified as independent risk factors for early mortality only in men. These findings should be considered when stratifying the risk for CABG patients.

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CHAPTER 3

3

Long-term survival after coronary artery bypass grafting is not sex-dependent

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Abstract

Objectives: Compared to men, women undergoing coronary artery bypass grafting have a higher morbidity and mortality, particularly in the early postoperative period. The aim of this study was to compare the patient profiles and long-term outcomes of men and women undergoing isolated coronary artery bypass grafting.

Material and Methods: We retrospectively reviewed all consecutive patients undergoing coronary bypass surgery between 1998 and 2015 in a single center (n=17,663). Multivariate logistic regression and propensity score-matched analyses (3,926 man and 3,926 women) were performed to analyze the independent risk factors for short-, medium- and long-term mortality. All data including preoperative and survival data were collected prospectively in a computerized database. Kaplan Meier curves and cox regression analysis were performed to investigate the difference between sexes regarding the long-term survival.

Results: The mean follow-up period was 9.6 ± 4.9 years. Compared with men, women were older (67.7 ± 9.4 vs. 63.9 ± 9.5, P<0.001) and had lower hemoglobin levels preoperatively. Early mortality (30-day) and 1-year mortality were significantly higher in women compared with men (1.8% vs. 2.8%; P<0.001 and 3.8% vs. 5.2%; P<0.001). Women showed a worse overall long-term survival (5,10, 15-year) than men. The propensity score-matched group revealed that female sex was not an independent risk factor for long-term mortality.

Conclusion: Women undergoing coronary artery bypass graft surgery have more comorbidities at surgical presentation compared with men, but propensity score-matched analysis suggests that female gender is not an independent risk factor for long-term survival.

Introduction

The overall number of female patients undergoing cardiac surgery is increasing each year [1]. In comparison with men, the overall outcome after cardiac surgery in women has shown to be less favorable [2]. Women referred for CABG are reported to have higher perioperative mortality and morbidity compared with men [3, 4]. Especially in younger women, a higher in-hospital, 30-day and post discharge mortality is reported [5, 6]. The perioperative outcomes have been attributed to a more acute and symptomatic stage of their disease at presentation. Additionally, women are known with smaller body surface area (BSA) with relatively smaller coronary arteries, a more advanced and diffuse stage of coronary artery disease and more common comorbidities including hypertension, dyslipidemia, diabetes, peripheral vascular disease (PVD) and chronic obstructive pulmonary disease (COPD) [7, 8].

3

Currently, there is an increasing awareness in the male-female differences in disease presentation and timing of diagnosis of coronary artery disease (CAD) [9, 10]. However, it remains controversial whether these differences in outcome are due to different risk profiles between men and women or whether female sex per sé is an independent risk factor of mortality. The focus of previous investigations has been primarily on in-hospital complications and mortality and only limited studies investigated the long-term outcomes, especially in the contemporary era [11-14]. The present study was designed to investigate the male-female differences in long-term outcomes after coronary artery bypass grafting.

Material and Methods

Patient selection

All data of patients who underwent isolated coronary artery bypass grafting (CABG), with or without the use of Extra-Corporal Circulation (ECC), between January 1998 and December 2015 in a single center (Catharina Hospital, Eindhoven, the Netherlands) were analyzed. Clinical data, including preoperative variables, intraoperative data and postoperative outcomes were collected prospectively and were retrieved from the computerized database of the department of Cardiothoracic Surgery. The institutional review board approved the study and waived the need for informed consent due to the observational character of the study.

Operative technique

All patients received short-acting anesthetic drugs to facilitate early extubating after revascularization. Conventional coronary artery bypass grafting was performed with normothermic, non-pulsatile flow extra-corporal circulation (ECC) and without ECC in off-pump coronary bypass grafting (OPCAB). According to the surgeon’s preference, cardioplegic arrest was accomplished by cold crystalloid solution (St Thomas’ solution) or warm blood cardioplegia. Conduit selection was chosen at surgeon's discretion. Operatives strategy (CABG vs OPCAB) was based on surgeon preference.

Study endpoints:

The primary end-point was defined as all-cause mortality during follow up (> 90 days postoperatively) and was derived from the municipal administration. Secondary outcomes included peri-operative mortality, peri-operative myocardial infarction and 30-day mortality. Data on the average age of death of the normal Dutch population (all-cause mortality) were extracted from the national Dutch statistics database.

Results

After analysis of our institutional database, 17,663 patients were included in the study. A total of 13,698 (77.6%) men and 3,965 (22.4%) women underwent isolated CABG during the study period. Compared with men, women were older (67.7 ± 9.4 years vs. 63.9 ± 9.5 years respectively; P<0.001) and had a lower hemoglobin level compared to men at the time of surgery (8.5 ±1.22 mmol/L vs. 8.6 ±1.17 mmol/L respectively; P=0.015). Preoperative comorbidities revealed a higher incidence of hypertension (57.6% vs 44.8%; P <0.001) and diabetes (28% vs 19.8%; P <0.001) in women than in men. Further characteristics are depicted in Table 1. In the matched cohort a total of 7,852 patients were included in our study, 3,926 female and 3,926 men.

In most patients, conventional CABG with use of ECC (84.7% in men, 83.4% in women) was performed. A significantly higher percentage of off-pump coronary artery bypass grafting (OPCAB) was performed in woman (16.1% vs 14.7%; P=0.03). No significant difference in ECC time, cross-clamp time and perioperative myocardial infarction was observed between the two groups. Re-exploration for bleeding or tamponade was higher in men than in women, as displayed in Table 2.

In the propensity matched groups OPCAB was significantly more performed in women (16.1% vs 14.5%; P=0.04), longer ECC time (58 min vs 61 min; P<0.001) and shorter aortic cross clamp time (38 min vs 40 min; P<0.001). Re-exploration was in the matched cohort also significantly lower in the female group compared to the male group (4.7% vs 6.0%; P=0.01, table 2).

The mean and median follow-up period of the survivors were 9.6 ± 4.9 years and 9.2 years (5.6 -13.5 years), respectively. Over the entire study period, 5054 patients died (28.6%), of whom 1342 were women and 3712 were men. Overall mortality was 27.1% in men and 33.8% in women (P < 0.001). Early mortality (ie. 30-day) and 1-year mortality were significantly

Table 1. Baseline characteristics total population and propensity matched groups

	Male n=13,689	**Female** n=3,965	**p-value**	**Matched Male** n=3,926	**Matched Female** n=3,926	**p-value**
Age, mean (±SD)	63.9 (±9.5)	67.7 (±9.4)	<0.0001	67.4 (±9.4)	67.7 (±9.4)	0.591
Hb, mean (±SD)	8.6 (±1.2)	8.5 (±1.2)	0.015	8.6 (±0.9)	8.6 (±0.9)	0.661
Hypertension, N (%)	6,143 (44.8%)	2,283 (57.6%)	<0.0001	2,290 (58.3%)	2,262 (57.6%)	0.537
COPD, N (%)	1,488 (10.9%)	457 (11.5%)	0.238	434 (11.1%)	449 (11.4%)	0.592
PVD, N (%)	1,706 (12.5%)	500 (12.6%)	0.807	505 (12.9%)	497 (12.7%)	0.813
CVA, N (%)	588 (4.3%)	180 (4.5%)	0.509	169 (4.3%)	180 (4.6%)	0.584
Diabetes, N (%)	2,718 (19.8%)	1,111 (28.0%)	<0.0001	1,098 (28.0%)	1,099 (28.0%)	0.980
EF <35%, N (%)	502 (3.7%)	120 (3.0%)	0.058	115 (2.9%)	119 (3.0%)	0.842
Creatinin, mean (±SD)	97.4 (±44.2)	96.3 (±39.1)	0.141	98.0 (±46.8)	97.0 (±38.5)	0.753
Dialysis, N (%)	34 (0.2%)	14 (0.4%)	0.297	9 (0.2%)	14 (0.4%)	0.404
Re-operation, N (%)	690 (5%)	206 (5.2%)	0.683	198 (5.0%)	204 (5.2%)	0.798

Hb: Hemoglobin (mmol/L), COPD: chronic obstructive pulmonary disease, PVD: peripheral vessel disease, CVA: cerebrovascular accident, EF<35%: lower left ventricular ejection fraction

higher in women compared with men; 30-day mortality (1.8% vs. 2.8%; P<0.001) and 1 year (3.8% vs. 5.2%; P<0.001). Compared with men, women had a worse 1-year, 3-year, 5-year, 10-year, and 15-year survival. (Figure A, Table 3). For the propensity matched groups survival was equal for women compared to men as seen in figure B and Table 3.

Univariate cox regression analysis identified female sex, age, hypertension, COPD, PVD, prior cerebrovascular accident (CVA), diabetes, lower left ventricular ejection fraction (<35 %) and renal impairment as significant risk factors for late mortality.

Univariate analysis identified off-pump coronary artery bypass (OPCAB) grafting to be correlated with lower late mortality. After adjustment for these confounding factors, multivariate analysis revealed female sex, age, hypertension, diabetes, PVD, COPD, prior CVA, left ventricular dysfunction as significantly associated with higher long-term mortality. For the matched cohort groups age, pre-operative Hb, COPD, PVD, CVA, diabetes, lower left ventricular ejection fraction (<35%) and impaired renal function are significant risk

Table 2. Surgical data total population and propensity matched groups

	Male n=13,698	Female n=3,965	p-value	Male n=3,926	Female n=3,926	p-value
CABG, N (%)	11,686 (85.3%)	3,326 (83.9%)	0.05	3,356 (85.5%)	3292 (83.9%)	0.07
OPCAB, N (%)	2,012 (14.7%)	639 (16,1)	0.03	570 (14.5%)	634 (16.1%)	0.04
ECC (min), median [IQR]	65 [51-82]	64 [33-54]	0.6	61 [45-79]	58 [41-77]	<0.001
X-clamp (min), median [IQR]	45 [33-57]	42 [33-54]	0.3	40 [29-55]	38 [26-51]	<0.001
Reexploration, N (%)	783 (5.7%)	189 (4.8%)	0.02	235 (6.0%)	185 (4.7%)	0.01
Perioperative MI, N (%)	376 (2.7%)	129 (3.3%)	0.1	123 (3.2%)	129 (3.3%)	0.80

CABG: coronary artery bypass grafting, OPCAB: off-pump coronary artery bypass grafting, ECC: extra corporal circulation, X-clamp: aortic cross clamp, MI: myocardial infarction

Table 3. Mortality total population and propensity matched groups

	Male n=13,698	Female n=3,965	p-value	Male n=3,926	Female n=3,926	p-value
1-year %	3.8%	5.2%	<0.001	4.7%	5.2%	0.35
3-year %	7.0%	8.7%	0.001	9.0%	8.7%	0.66
5-year %	10.6%	12.3%	0.003	12.9%	12.3%	0.42
10-year %	19.9%	24.2%	<0.001	24.0%	24.2%	0.98
15-year %	25.7%	32.0%	<0.001	30.1	32.0	0.07

factors for late mortality as female sex, hypertension, reoperation and OPCAB are not. Multivariate analysis for these factors showed that older age, lower Hb, COPD, PVD, prior CVA, diabetes, EF<35% and impaired creatinine levels are associated with higher long-term mortality (Table 5).

Discussion

The current study investigated the long-term outcomes of coronary artery bypass grafting in 17,663 patients with a median follow up of more than 9 years. At the time of surgery, women presented at an older age and showed a higher risk-profile in comparison with men. We found a significantly higher incidence of both early (30-day) mortality, 1-year and long-term mortality in the female population compared to the male population. Survival analysis identified age, COPD, PVD, CVA, diabetes mellitus, decreased ejection fraction and decrease

Table 4. Univariate and Multivariate analysis the total population

Univariate analysis	HR (95%)	p-value	Multivariate analysis	HR (95%)	p-value
Female gender	1.28 (1.20-1.36)	<0.0001	Female gender	1.08 (1.01-1.15)	0.03
Age	1.09 (1.08-1.09)	<0.0001	Age	1.09 (1.08-1.09)	<0.0001
Hb	0.98 (0.96-1.00)	0.07			
Hypertension	1.12 (1.05-1.18)	<0.0001	Hypertension	0.95 (0.90-1.00)	0.07
COPD	1.78 (1.65-1.91)	<0.0001	COPD	1.53 (1.42-1.65)	<0.0001
PVD	2.16 (2.02-2.32)	<0.0001	PVD	1.76 (1.64-1.89)	<0.0001
CVA	1.81 (1.61-2.03)	<0.0001	CVA	1.31 (1.18-1.48)	<0.0001
Diabetes	1.66 (1.56-1.76)	<0.0001	Diabetes	1.47 (1.38-1.56)	<0.0001
EF<35%	2.66 (2.38-2.98)	<0.0001	EF<35%	2.6 (2.32-2.90)	<0.0001
Creatinine	1.00 (1.00-1.00)	0.001	Creatinine	1.00 (1.00-1.00)	0.004
Re-operation	1.11 (0.99-1.24)	0.06			
OPCAB	0.88 (0.81-0.95)	0.002	OPCAB	1.07 (0.97-1.16)	0.1

Hb: Hemoglobin (mmol/L), COPD: chronic obstructive pulmonary disease, PVD: peripheral vessel disease, CVA: cerebrovascular accident, EF<35%: lower left ventricular ejection fraction, OPCAB: off-pump coronary artery bypass grafting

kidney function as risk-factors for late mortality. After adjustment for the baseline clinical parameters of men and women using propensity score matching, the same risk factors, as mentioned above were identified. Female sex was a risk factor for late mortality in the CABG group, but in contrast the propensity matched group showed that was no difference in late mortality between men and women. The large Chinese population study from Wang et al. concluded that female sex was not an independent risk factor for in-hospital mortality and long-term mortality [15]. This could mean that the lower long-term survival observed in the female population is mainly attributed to the associated risk factors which are significantly more encountered in women than in men.

Previous researchers have proposed that women with (premature) coronary artery disease (CAD) have unknown risk factors or lack protective factors [16,17]. Several genetic and

Table 5. Univariate and Multivariate analysis propensity matched groups

Univariate Analysis	HR (95%)	p-value	Multivariate analysis	HR (95%)	p-value
Female Gender	0.99 (0.91-1.06)	0.696			
Age	1.08 (1.08-1.09)	<0.0001	Age	1.08 (1.08-1.09)	<0.0001
Hb	0.95 (0.91-0.99)	0.03	Hb	0.96 (0.92-0.99)	0.04
Hypertension	1.07 (0.99-1.16)	0.1			
COPD	1.67 (1.51-1.86)	<0.0001	COPD	1.54 (1.39-1.71)	<0.0001
PVD	1.98 (1.79-2.19)	<0.0001	PVD	1.74 (1.58-1.93)	<0.0001
CVA	1.73 (1.47-2.04)	<0.0001	CVA	1.37 (1.16-1.61)	<0.0001
Diabetes	1.63 (1.50-1.77)	<0.0001	Diabetes	1.48 (1.36-1.61)	<0.0001
EF<35%	2.39 (2.01-2.86)	<0.0001	EF<35%	2.70 (2.26-3.22)	<0.0001
Creatinine	1.01 (1.01-1.02)	<0.0001	Creatinine	1.01 (1.01-1.01)	0.01
Re-operation	1.03 (0.88-1.21)	0.69			
OPCAB	0.90 (0.80-1.01)	0.07			

Hb: Hemoglobin (mmol/L), COPD: chronic obstructive pulmonary disease, PVD: peripheral vessel disease, CVA: cerebrovascular accident, EF<35%: lower left ventricular ejection fraction, OPCAB: off-pump coronary artery bypass grafting

hormonal pathways have been hypothesized, including abnormalities of the estrogen receptor, premature menopause, ovarian dysfunction and proinflammatory properties of hormone replacement therapy [18]. The varying hormonal levels in women, are also linked to other (vascular) disorders like migraine headaches, Raynaud's phenomenon and autoimmune arteritis, from which women disproportionately suffer compared to men.

Recently, more research has focused on the pathophysiology of CAD in woman [19-22]. Compared to men, women suffer more from microvascular dysfunction which could be the basis of premature coronary artery disease. In these patients, coronary arteries disease arises from a dysfunctional microcirculation. Coronary microvascular dysfunction is present in approximately one half of women with chest pain in the absence of obstructive CAD and cannot be predicted by risk factors for atherosclerosis and hormone levels [23]. Among women with suspected ischemia and atherosclerosis risk factors, coronary microvascular reactivity to adenosine significantly improves prediction of major adverse outcomes over angiographic CAD severity and CAD risk factors. These findings suggest that coronary micro vessels represent novel targets for diagnostic and therapeutic strategies. [24]. Smaller body surface area and smaller coronary arteries, as seen in woman, have been postulated as a cause of reduced graft patency rates in CABG. In literature, inconstancy regarding female body size can be found. The independent influence of body size on outcome is not well established [11, 25]. In addition, a referral bias might also play a role, if women with symptoms of coronary heart disease are being referred less often or later than men [26].

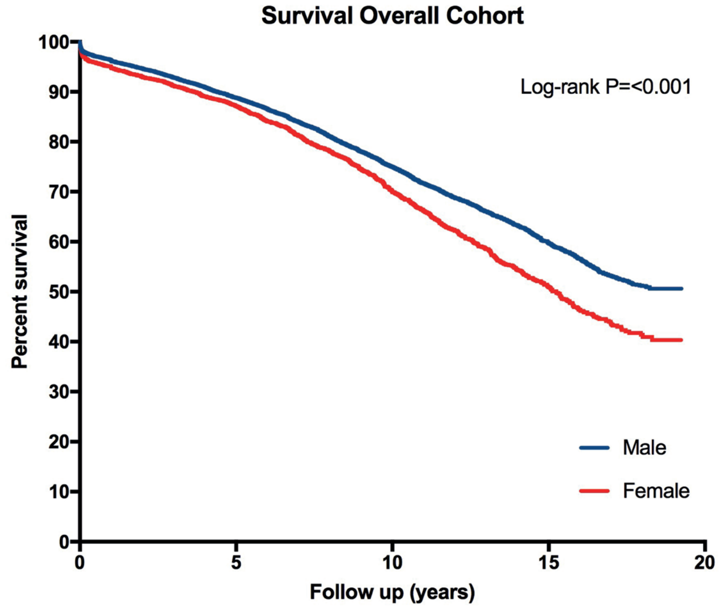

Figure 1: Survival total population

Previous studies have shown lower survival rates after CABG in women than in men [6,7,11,12]. In the present analysis, the poorer long-term survival in women after CABG in the total group of CABG patients might reflect the relatively poorer survival of young female patients. There is a survival benefit for older woman undergoing CABG, this is in accordance with the better life expectancy of women in the general population. A possible explanation for a higher mortality in young women could be the impact of different risk factors. While smoking boosts the likelihood of acute myocardial infarction (AMI) in both men and woman of all ages, it has much more powerful effect in younger women, especially those under 50 as reported recently [27]. Unfortunately, the present study didn't collect data concerning smoking as a preoperative risk factor. However, the analysis showed a significant higher incidence of COPD young woman. Furthermore, a higher incidence of PVD and CVA were observed in the younger age group, which are related to smoking. Recent investigators have reported that young women presenting with AMI have a lower likelihood of adherence to the guidelines concerning AMI therapies [28]. It is possible that young women undergoing CABG are less adherent to the guidelines concerning long-term therapies such as statins and anti-platelet therapy.

3

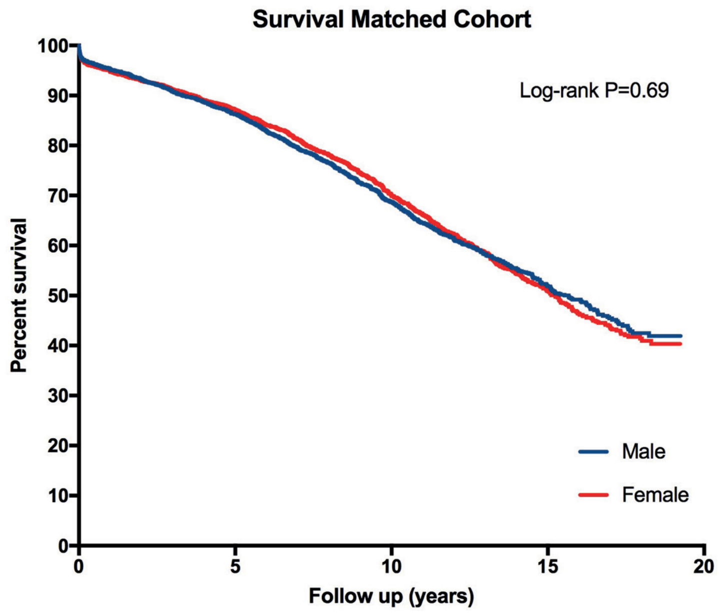

Figure 2: Survival propensity matched groups

Limitations

The study is limited by the retrospective design and its accompanied disadvantages. The relatively long study period (18 years) is automatically prone to technical progress, especially in percutaneous techniques, which could have led to differences in referrals. Another limitation is the relatively small proportion of women in comparison with men in the study (13,698 men vs 3,965 women), but propensity score matching (3,926 men and 3,926 women) should have excluded selection bias.

Conclusion

Women undergoing coronary artery bypass grafting surgery have more comorbidities at surgical presentation compared with men. Women have a higher operative mortality but comparable long-term survival than men after coronary bypass surgery in this large propensity matched group. Further research is warranted to discover unknown risk factors and investigated the lack of protective factors in women.

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CHAPTER 4

4

Do women benefit more than men from off-pump coronary artery bypass grafting?

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Abstract

Objectives
Outcomes after coronary artery bypass grafting (CABG) are worse in women than in men. This study aims to investigate whether off-pump coronary artery bypass (OPCAB) surgery improves the outcomes in women by comparing different outcome measures in both genders.

Methods
Patients who underwent isolated CABG, either on-pump (ONCAB) or OPCAB, between January 1998 and June 2017 were included. Primary endpoints were 30-day and 120-day mortality. Logistic regression models were constructed to evaluate the effect of the CABG technique on important outcomes such as mortality and the need for blood transfusion.

Results
The data of 17,052 patients were analyzed, 3,684 of whom were women (414 OPCAB) and 13,368 men (1,483 OPCAB). The mean number of grafts was lower in the OPCAB group of both genders ($p < 0.001$). Postoperatively, both men and women undergoing OPCAB surgery received fewer red blood cell transfusions ($p < 0.001$) and had higher postoperative hemoglobin levels ($p < 0.001$) than those undergoing ONCAB. Early mortality occurred less frequently after OPCAB surgery in both genders, although the difference was not significant. However, 120-day mortality was significantly lower after OPCAB surgery in women, even after correction for preoperative risk factors [odds ratio (OR) = 0.356, 95% confidence interval (CI) 0.144–0.882, $p = 0.026$]. The difference in 120-day mortality was not significant in men (OR = 0.787, 95% CI 0.498–1.246, $p = 0.307$).

Conclusions
Women undergoing CABG benefit more from OPCAB surgery than from ONCAB surgery in terms of 120-day mortality. This difference was not found in men in our patient population.
What's new?

- In female patients undergoing coronary artery bypass grafting (CABG), the adjusted 120-day mortality after off-pump CABG is significantly lower than that after on-pump CABG. This finding was not demonstrated in the male population undergoing CABG.
- In both male and female populations undergoing CABG, a lower rate of postoperative blood transfusions and a higher postoperative hemoglobin level are demonstrated after the off-pump technique compared to the on-pump technique.

Introduction

Female patients have higher operative morbidity and mortality than males after coronary artery bypass grafting (CABG) [1,2,3,4]. It has been claimed that these variations in outcomes could be attributed to different revascularization strategies [5]. Previous studies have also shown that women who underwent CABG were older and had more co-morbidities, such as diabetes, hyperlipidemia, hypertension and congestive heart failure, than men [1, 4, 6,7,8,9]. Moreover, female gender is scored as a risk factor for adverse outcomes after CABG in frequently used scoring systems, such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE) [10] and the Society of Thoracic Surgeons (STS) [11] score. Off-pump coronary artery bypass grafting (OPCAB) has been shown to improve the outcome particularly in high-risk patients [12]. Some previous studies have shown a beneficial effect of OPCAB surgery for women [2, 3, 6, 13, 14]. Although much research has been conducted concerning the outcomes after ONCAB and OPCAB surgery in women, results are conflicting and no recent data are available. Also, previous research has mainly focused on early and in-hospital mortality, which might not be an accurate outcome measurement for cardiac surgery [15, 16]. The aim of the present study was to determine if women benefit more from OPCAB than from ONCAB surgery by comparing the outcomes of these techniques in both genders.

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Methods

This study included all patients who underwent isolated CABG, either ONCAB or OPCAB, between January 1998 and June 2017 at our institution (Catharina Hospital Eindhoven, The Netherlands). In order to minimize the heterogeneity of the population, patients were excluded if they had single-vessel disease, if they had undergone prior cardiac surgery, or if they had had an on-pump beating heart operation without aortic cross clamping. Clinical data, including patient demographics, complications and mortality, were extracted from a computerized database of the Department of Cardiothoracic Surgery. Preoperative variables included age, underweight [body mass index (BMI) <20 kg/m^2], obesity (BMI ≥30 kg/m^2), hypertension, chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), diabetes mellitus, left ventricular ejection fraction (LVEF) <35%, hemoglobin level, estimated glomerular filtration rate (eGFR, calculated using the Modification of Diet in Renal Disease formula [17]) and triple-vessel disease. The ethics committee of our institution approved our study protocol and waived the need for informed consent.

The primary endpoints were early mortality (within 30 days postoperatively) and 120-day mortality, data obtained from the municipal administration (*Gemeentelijke Basisadministratie*). Secondary in-hospital endpoints included cerebrovascular accident (CVA), transient ischemic attack (TIA)/reversible ischemic neurological deficit (RIND), myocardial infarction, blood product transfusions (≥1 packed cells) during hospital stay, re-exploration for bleeding and postoperative hemoglobin level (data obtained the day before discharge, 2–5 days after surgery).

The decision to use the off-pump technique was made by the surgeon and did not follow certain selection criteria. Our standard policy to stop preoperative anticoagulant therapy was applied to the whole patient population throughout the study period. In patients receiving preoperative dual anti-platelet therapy, acetylsalicylic acid (aspirin) was continued until the time of the operation, while P2Y12 inhibitors were stopped 5 days preoperatively.

In both ONCAB and OPCAB surgery, all patients received short-acting anesthesia to facilitate rapid extubation. In ONCAB surgery, the extracorporeal circulation (ECC) was normothermic with a non-pulsatile flow; cardioplegic arrest was accomplished by the use of cold crystalloid cardioplegia (St. Thomas' solution) or warm blood cardioplegia, according to the surgeon's preference. In OPCAB surgery a gauze sling was temporarily fixed to the deepest point of the pericardium for maximum exposure of the heart or a vacuum-assisted apical suction device (Starfish, Medtronic, Eindhoven, The Netherlands) was used. A suction device (Octopus, Medtronic) to immobilize the target vessel and an intracoronary shunt (ClearView Shunt, Medtronic) were used. Since 2003, cell salvage has been used in all patients undergoing CABG, whether OPCAB or ONCAB surgery.

Statistical analysis

Patients were divided into groups based on gender and subsequently divided into subgroups based on the type of surgery (ONCAB or OPCAB). To compare categorical variables, the chi-square or Fisher's exact test was used, and figures are presented as numbers and percentages. Skewness and kurtosis were used to explore normality for continuous variables. Normally distributed variables were compared by the independent samples *t*-test and are presented as mean ± standard deviation (SD). Non-normally distributed variables were compared by the Mann-Whitney test and are presented as median and interquartile range (IQR, 25% and 75%). To identify the effect of OPCAB surgery on significant postoperative outcomes, separate regression analyses were performed. In these models, type of surgery was the independent variable with ONCAB as reference; the outcome was the dependent variable. For the categorical outcomes early mortality, 120-day mortality, red blood cell transfusion and re-exploration, logistic regression was performed. For the continuous outcome postoperative hemoglobin level, linear regression analysis was performed. When odds ratios in the univariate analysis were significant, a multivariable analysis was performed with correction for differences in preoperative variables. A p-value of less than 0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics 24 (SPSS Inc., Chicago, IL, USA).

Results

The data of 3,684 women (3,270 ONCAB and 414 OPCAB) and 13,368 men (11,885 ONCAB and 1,483 OPCAB) were analyzed. Preoperative patient characteristics are presented in Tab. 1. Both women and men undergoing OPCAB surgery were younger (women: ONCAB 68.8 years vs OPCAB 67.6 years, p = 0.021; men: ONCAB 64.7 years vs OPCAB 64.0 years, p = 0.011), had a relatively better LVEF (women: ONCAB 3.0% vs OPCAB 1.0%, p = 0.017; men ONCAB 3.5% vs OPCAB 2.2%, p = 0.007) and presented less often with triple-vessel disease (women: ONCAB 60.0% vs OPCAB 36.5%, p < 0.001; men: ONCAB 64.9% vs OPCAB 41.6%, p < 0.001). More women undergoing OPCAB surgery were obese (p = 0.040), but fewer were diabetic

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Table 1. Preoperative characteristics of patients undergoing ONCAB and OPCAB surgery

	Women n=3,684			**Men** n=13,368		
	ONCAB n=3,270	**OPCAB** n=414	**p-value**	**ONCAB** n=11,885	**OPCAB** n=1,483	**p-value**
Age in years, mean ±SD	68.8 ±8.8	67.6 ± 10.2	0.021	64.7 ±9.4	64.0 ±10.1	0.011
Underweight (BMI < 20 kg/m²)	78 (2.4%)	5 (1.2%)	0.128	94 (0.8%)	17 (1.1%)	0.155
Obese (BMI ≥ 30 kg/m²)	886 (27.1%)	132 (31.9%)	0.040	2,349 (19.8%)	293 (19.8%)	0.995
Hypertension	1,930 (59.0%)	259 (62.6%)	0.167	5,474 (46.1%)	732 (49.4%)	0.016
COPD	398 (12.2%)	44 (10.6%)	0.363	1,253 (10.5%)	144 (9.7%)	0.323
PVD	422 (12.9%)	60 (14.5%)	0.367	1,469 (12.4%)	200 (13.5%)	0.216
Prior CVA	151 (4.6%)	19 (4.6%)	0.979	511 (4.3%)	62 (4.2%)	0.831
Diabetes mellitus	965 (29.5%)	101 (24.4%)	0.031	2,427 (20.4%)	289 (19.5%)	0.400
LVEF < 35%	99 (3.0%)	4 (1.0%)	0.017	416 (3.5%)	32 (2.2%)	0.007
Preoperative hemoglobin level, mmol/L, mean ±SD	8.0 ±0.8	8.1±0.8	0.312	8.8 ±0.8	8.8 ±0.8	0.935
eGFR in mL/min/ 1.73 m², median (IQR)	59.7 (49.9-72.0)	61.1 (52.2-73.2)	0.116	68.8 (59.4-80.0)	70.4 (61.2-81.8)	0.001
3-vessel disease, including main stem stenosis	1,962 (60.0%)	151 (36.5%)	<0.001	7,715 (64.9%)	617 (41.6%)	<0.001

Categorical variables are presented as percentages; continuous variables are presented as mean ± SD or median (IQR); IQR: interquartile range (25-75%); SD: standard deviation BMI: body mass index; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; eGFR: estimated glomerular filtration rate, calculated by using the MDRD (Modification of Diet in Renal Disease) formula; LVEF: left ventricular ejection fraction; PVD: peripheral vascular disease.

(p = 0.031). More men undergoing OPCAB surgery suffered from hypertension (p = 0.016). The male OPCAB group had a higher eGFR than the male ONCAB group (p = 0.001). Tab. 2 (operative data) shows that the mean number of grafts was significantly lower in the OPCAB group compared to the ONCAB group in both women and men (both p < 0.001).

Tab. 3 presents the outcomes of men and women after ONCAB and OPCAB surgery. After OPCAB surgery, both men and women received fewer red blood cell transfusions (women: ONCAB 61.6% vs OPCAB 25.4%; men: ONCAB 22.5% vs OPCAB 10.0%, both p < 0.001) and had a higher postoperative hemoglobin level (women: ONCAB 6.8 vs OPCAB 7.1 mmol/l, *p* < 0.001; men: ONCAB 7.1 vs OPCAB 7.6 mmol/l, p < 0.001). In men, re-exploration for bleeding was performed significantly less frequently in the OPCAB group than in the ONCAB group (p = 0.002). This difference was not significant for women (p = 0.202). Early mortality did not differ significantly between the two types of surgery in either group (women: ONCAB 2.4% vs OPCAB 1.0%, p = 0.057; men: ONCAB 1.4% vs OPCAB 0.8%, *p* = 0.080). However, 120-day mortality was significantly lower in women after OPCAB surgery compared to

Table 2. Operative data of patients undergoing ONCAB and OPCAB surgery

	Women n=3684			**Men** n=13368		
	ONCAB n=3270	**OPCAB** n=414	**p-value**	**ONCAB** n=11,885	**OPCAB** n=1,483	**p-value**
Number of grafts, mean ±SD	3.5±0.9	2.7±0.8	<0.001	3.7±0.9	2.9±0.8	<0.001
ICOR, mean ±SD	1.35±0.33	1.15±0.24	<0.001	1.42±0.33	1.19±0.26	<0.001

Continuous variables are presented as mean ± SD. ICOR: index of completeness of revascularization

Table 3: Postoperative outcomes of patients undergoing ONCAB and OPCAB surgery

	Women n=3,684			**Men** n=13,368		
	ONCAB n=3,270	**OPCAB** n=414	**p-value**	**ONCAB** n=11,885	**OPCAB** n=1,483	**p-value**
CVA	36 (1.1%)	3 (0.7%)	0.617	76 (0.6%)	6 (0.4%)	0.275
TIA/RIND	10 (0.3%)	0 (0.0%)	0.615	27 (0.2%)	0 (0.0%)	0.066
Myocardial infarction	98 (3.0%)	16 (3.9%)	0.337	260 (2.2%)	37 (2.5%)	0.449
Red blood cell transfusion	2,015 (61.6%)	105 (25.4%)	<0.001	2,679 (22.5%)	148 (10.0%)	<0.001
Re-exploration for bleeding	60 (1.8%)	4 (1.0%)	0.202	368 (3.1%)	25 (1.7%)	0.002
Postoperative hemoglobin level, mmol/L, mean ±SD	6.8 ±0.7	7.1 ±0.8	<0.001	7.1 ±0.8	7.6 ±0.9	<0.001
30-day mortality	80 (2.4%)	4 (1.0%)	0.057	161 (1.4%)	12 (0.8%)	0.080
120-day mortality	119 (3.6%)	5 (1.2%)	0.010	232 (2.0%)	21 (1.4%)	0.153

Categorical variables are presented as percentages; continuous variables are presented as mean ± SD or median (IQR); IQR: interquartile range (25-75%); SD: standard deviation. CVA: cerebrovascular accident; RIND: reversible ischemic neurological deficit; TIA: transient ischemic attack

ONCAB surgery (ONCAB 3.6% vs OPCAB 1.2%, p = 0.010), but this was not the case for men (ONCAB 2.0% vs OPCAB 1.4%, p = 0.153).

Tab. 4 presents the multivariable logistic regression analysis for mortality, red blood cell transfusion and re-exploration for bleeding, corrected for significantly different preoperative risk factors. These confounders include age, obesity, diabetes mellitus, LVEF <35%, COPD, emergency, PVD and triple-vessel disease. In both groups, 30-day mortality was not significantly different between OPCAB and ONCAB surgery [women: odds ratio (OR) = 0.429, 95% confidence interval (CI) 0.155–1.189, p = 0.104; men: OR = 0.641, 95% CI 0.352–1.165, p = 0.145]. In women, 120-day mortality was lower in the OPCAB group compared to the ONCAB group (OR = 0.356, 95% CI 0.144–0.882, p = 0.026). This difference in 120-day mortality between OPCAB and ONCAB surgery was not significant in men (OR = 0.787, 95% CI 0.498–1.246, p = 0.307). In both men and women, OPCAB surgery was associated with fewer red blood cell transfusions (p < 0.001). Tab. 5 shows the multivariable linear regression analysis of postoperative hemoglobin levels, corrected for significant preoperative risk factors. After OPCAB surgery, hemoglobin levels were higher in both men and women compared to ONCAB surgery (p < 0.001).

Table 4. Multivariable logistic regression analysis of significant outcomes after OPCAB versus ONCAB surgery (ONCAB surgery is reference group)

	Women n=3,684		**Men** n=13,368	
	Multivariable* OR (95% CI)	**p-value**	**Multivariable** OR (95% CI)**	**p-value**
30-day mortality	0.429 (0.155-1.189)	0.104	0.641 (0.352-1.165)	0.145
120-day mortality	0.356 (0.144-0.882)	0.026	0.787 (0.498-1.246)	0.307
Red blood cell transfusion	0.212 (0.167-0.270)	<0.001	0.394 (0.330-0.471)	<0.001
Re-exploration for bleeding	0.542 (0.194-1.512)	0.242	0.524 (0.347-0.791)	0.002

* multivariable model corrected for age, obesity, diabetes mellitus, LVEF<35 and triple vessel disease
** multivariable model corrected for age, hypertension, LVEF<35, eGFR and triple vessel disease

Table 5. Multivariable linear regression analysis of postoperative hemoglobin after OPCAB versus ONCAB surgery (ONCAB surgery is reference group)

	Women n=3,684		**Men** n=13,368	
	Multivariable* B (95% CI)	**p-value**	**Multivariable** B (95% CI)**	**p-value**
Postoperative hemoglobin level, mmol/L	0.256 (0.182-0.331)	<0.001	0.500 (0.457-0.544)	<0.001

* multivariable model corrected for age, obesity, diabetes mellitus, LVEF<35 and triple vessel disease
** multivariable model corrected for age, hypertension, LVEF<35, eGFR and triple vessel disease

Discussion

The present study investigated whether women benefit more from OPCAB than from ONCAB surgery and whether the gender difference plays a role in outcomes after these techniques. This analysis showed lower early mortality after OPCAB than after ONCAB surgery in both genders, although the difference was not statistically significant. After OPCAB surgery, 120-day mortality was significantly lower in women, but this difference was not significant in men. After OPCAB surgery, both women and men had higher hemoglobin levels, which was reflected in lower rates of red blood cell transfusions.

Our findings are in agreement with the findings of a meta-analysis by Attaran et al. [8]. However, in contrast to Attaran et al., who reported a higher 30-day mortality in the OPCAB group (4.8%) than in the ONCAB group (0.7%), we found a lower 30-day mortality in the OPCAB groups. Mack et al. [18] retrospectively analyzed the data of 7,374 (3,688 pairs of) women after ONCAB or OPCAB surgery and concluded that women had higher corrected operative mortality (OR 1.733, $p = 0.002$) after ONCAB surgery compared to OPCAB surgery. Bucerius et al. [1] showed in 2,182 consecutive patients (152 of whom underwent OPCAB surgery) that OPCAB surgery is associated with a significantly reduced 30-day mortality (OR 0.11, $p = 0.032$) compared to ONCAB surgery.

The finding that women seem to benefit more from the elimination of cardiopulmonary bypass than men has been reported previously. Fu et al. [7], who conducted a retrospective analysis of 5,359 patients who had undergone ONCAB or OPCAB surgery, concluded that OPCAB surgery resulted in lower early mortality, especially in women. Moreover, Puskas and colleagues [2, 13, 14] have shown repeatedly that OPCAB surgery is associated with significantly lower risk-adjusted in-hospital mortality compared to ONCAB surgery, especially in women. The fact that no significant difference was found in 30-day mortality in women in our study might be due to the number of events being too small to reach statistical significance.

In contrast to previous studies, we evaluated 120-day mortality, which was significantly lower in women undergoing OPCAB surgery than in those undergoing ONCAB surgery. Recently, it has been suggested that 30-day mortality might not be an optimal outcome measurement in cardiac surgery, as survival curves stabilize after 60–120 days, depending on the type of intervention [15]. Also, our institution is affiliated with an academic national Dutch registry program (*Meetbaar Beter*) [16]. This registry was developed to improve the quality and to stimulate the transparency of data publication in cardiac care. This program chose 120-day mortality instead of 30-day mortality as an outcome variable for quality purposes after CABG [16]. The aim of our study was limited to short-term outcomes, including both 30-day and 120-day mortality. These outcomes are directly affected by the technical aspects of the procedure, including the use of the ECC (OPCAB vs ONCAB). Longer-term outcomes such as 1-year mortality have less correlation with the operative technique, especially when using all-cause mortality as an outcome.

In the present study, we were not able to retrieve data on the cause of death in order to clarify the benefit of OPCAB in the female population. However, the difference in mortality between OPCAB and ONCAB surgery in women might be reflected by a difference in the number of red blood cell transfusions between the OPCAB and ONCAB groups, as red blood cell transfusion is associated with increased early mortality [19]. Early reports of OPCAB surgery [20] recommended using this technique particularly in high-risk patients who are more liable to ECC complications. Considering that women have relatively more risk factors than men, avoiding the ECC would be more beneficial in women than in men. Nuttall et al. [21] demonstrated that OPCAB surgery reduces perioperative bleeding and is associated with an overall reduction in allogenic transfusion requirement [21]. In earlier studies, female gender was an independent factor associated with perioperative blood transfusion after CABG [22, 23]. Most of these studies' populations included CABG patients with use of the ECC. In the study of Arora et al. [22], the transfusion rate was 17.3% when using the ECC and 2.7% for OPCAB cases. This means that avoiding the ECC in female patients is more beneficial with regard to transfusions than in male patients. Among others, Karkouti et al. [23] concluded that the influence of gender on the risk of transfusion is due to the smaller blood volume in women. The effect of hemodilution of the ECC is more pronounced in women, which is reflected in the fact that women benefit more from OPCAB surgery than men. Other side-effects of the ECC are possibly tolerated less well by women than by men, including coagulopathy, complement activation and neurological complications [21]. The smaller body surface area in women is an additional factor that might increase the risk of bleeding after the use of the ECC [24].

We found no significant difference regarding postoperative CVA, TIA/RIND and myocardial infarction after OPCAB and ONCAB surgery, which is in line with some previous studies performed in women [1, 18]. Although we found no statistically significant difference in postoperative CVA and TIA/RIND after OPCAB or ONCAB surgery, OPCAB surgery was associated with fewer neurological complications in both men and women. In our internal quality assessment, we considered such a difference to be clinically significant even in the absence of statistical significance (women: 0.7% in OPCAB compared to 1.4% in ONCAB; men: 0.4% in OPCAB compared to 0.8% in ONCAB). This is in line with previous studies, which have shown that OPCAB surgery is associated with fewer postoperative neurological adverse events than ONCAB surgery [14, 25,26,27]. We found no significant difference in the incidence of postoperative myocardial infarction in our population. Previous studies reported a significantly lower incidence of myocardial infarction and major adverse cardiac

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events after OPCAB surgery compared to ONCAB surgery [13, 26]. Our finding might be explained by the relatively small number of events.

In our population, we observed that the rate of re-exploration for bleeding was significantly lower after OPCAB surgery compared to ONCAB surgery in men, but this difference was not significant in women. However, in both genders, the re-exploration rate was nearly twice as high in the ONCAB group as in the OPCAB group. In a retrospective study of 3,771 patients, Karthik and colleagues [28] reported less re-exploration for bleeding after OPCAB surgery, although the difference was not significant (3.0% in the OPCAB group compared to 4.4% in the OPCAB group after propensity score matching, $p = 0.22$). In this respect, OPCAB surgery has a different heparinization policy, apart from avoiding other adverse effects of the ECC such as complement activation [29] and coagulopathy [30].

Our study has some limitations. First, because of the retrospective design, we cannot exclude selection bias and a possible lack of variables that could have influenced the results. For instance, data on preoperative anticoagulant therapy are lacking. This factor could have affected the incidence of postoperative bleeding and consequently blood transfusion. Second, the primary outcome measures were all-cause mortality and we did not retrieve data on the cause of death. However, death within 120 days postoperatively is most likely a consequence of surgery. During the study period of almost 20 years, many surgical, ECC and anesthetic techniques have evolved that could have influenced the outcomes as well. New implementations in ECC techniques and blood management programs have led to better outcomes after CABG, especially in terms of postoperative blood loss and hemoglobin levels. Women have possibly benefitted more than men from such blood conservation programs with more substantial improvement in the outcome. As we mentioned above, the choice between the two techniques was made by the individual surgeon and was not done following certain selection criteria. However, surgical bias cannot be excluded because some surgeons *always* performed OPCAB and the others *always* performed ONCAB.

In conclusion, women undergoing CABG seem to benefit more from OPCAB surgery than from ONCAB surgery in terms of a lower 120-day mortality. An important correlated finding is that women require fewer blood cell transfusions after OPCAB surgery.

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CHAPTER 5

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Impact of sex on the outcome of isolated aortic valve replacement and the role of different preoperative profiles

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Objective: The aim of this study was to compare the patient profiles and outcomes of men and women undergoing isolated aortic valve replacement.

Design: Patient data were retrospectively analyzed.

Setting: This single-center study was performed in the Catharina Hospital (Eindhoven).

Participants: 2362 patients, 1040 (44%) of whom were women and 1322 were men (56%).

Interventions: Isolated aortic valve replacement was performed between January 1998 and December 2016.

Measurements and Main Results: The mean follow-up was 8.3 ±5.1 years. Women were relatively older (69.9 years vs. 64.6 years, p<0.001), more of them were underweight, obese and diabetic, they had lower hemoglobin and worse renal function than men. However, less women suffered from chronic obstructive pulmonary disease, aortic regurgitation, left ventricular dysfunction and endocarditis than men. Early mortality did not significantly differ between men and women (p=0.238). Overall survival was worse in women (p<0.001). After correction for potential risk factors, female gender was not associated with worse survival. In the study period, the mean age of patients undergoing AVR increased. Also, the mean age at the time of death increased, following the trend of national statistics.

Conclusions: Although women have relatively more risk factors than men, early mortality in women is not significantly higher than in men. In addition, the overall survival is worse in women than in men. After adjustment for preoperative risk factors, there is no difference in overall survival between women and men.

Key words: aortic valve replacement surgery, sex, mortality

Introduction

Sex-specific differences in cardiovascular diseases have been studied in the past [1]. In the majority of studies on coronary artery bypass graft surgery (CABG) with or without associated valve surgery, women had less favorable perioperative and postoperative outcomes [2-5]. However, men and women undergoing CABG have different preoperative patient profiles. Also, the predictive value of known risk factors of early mortality is sex dependent [4]. In case of isolated aortic valve replacement (AVR), results are more controversial [3, 6-10]. Two recent studies indicated that in comparison to men, women have different risk profiles and demographics, a higher incidence of vascular complications and blood transfusions and higher in-hospital mortality after AVR [1, 11]. Female sex is one of the risk factors for unfavorable outcomes in predictive models that estimate perioperative mortality after cardiac surgery, such as the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) [12] in Europe and the Society of Thoracic Surgeons (STS) score [13] in north America 8. However, these models were originally designed for CABG populations [14]. In case of AVR, it has been reported that the EuroSCORE underestimates the risk of operative mortality in high-risk patients and that the STS score overestimates this risk in low risk patients [14, 15]. To date, long-term follow-up data after AVR in both sexes are sparse [1, 3, 6]. The present study was designed to compare the patient profiles and outcomes of men and women who underwent AVR between 1998 and 2016 in the Department of Cardiothoracic Surgery, Catharina Hospital, Eindhoven, the Netherlands.

Methods

Population and study Data

In this study, data of patients who underwent isolated AVR between January 1998 and December 2016 in a single center (Catharina Hospital, Eindhoven, the Netherlands) were analyzed. Patients undergoing reoperation were excluded to avoid duplicate data. Data were retrieved from the computerized database of the Department of Cardiothoracic Surgery, including data on patient characteristics, operative data, complications and survival. Baseline characteristics included known risk factors. The study protocol was endorsed by the ethics committee of our institution, which waived the need for informed consent.

End points and follow-up evaluation

The primary end point was all-cause mortality during the follow-up period, which was correlated to mortality data from the municipal administration ('Gemeentelijke Basisadministratie'). Data about average age of death of the normal Dutch population all-cause mortality) were extracted from the national Dutch statistics database (Centraal Bureau voor de Statistiek, (CBS)) (16). Secondary outcomes included early mortality (within

30 days postoperatively), re-exploration, blood product transfusions, cerebrovascular accident (CVA), transient ischemic attack (TIA) and myocardial infarction during hospital stay as extracted from the database.

Operative techniques

In AVR surgery, all patients received short-acting anesthesia to facilitate early extubation. The extracorporeal circulation (ECC) was normothermic with a non-pulsatile flow. Cardioplegic arrest was accomplished with the use of cold crystalloid cardioplegia (St Thomas' solution) or warm blood cardioplegia, according to the surgeon's preference. The type of prosthesis (mechanical or biological) was chosen by the surgeon and the patient together.

Statistical analyses

Categorical variables were presented as numbers and percentages and compared with the chi-square test or Fisher's Exact test. For continuous variables, normality was explored using skewness and kurtosis. In case of normal distribution, variables were presented as means ± standard deviation (SD) and compared with the independent samples t-test. In case of non-normal distribution, median and interquartile range (interquartile range (IQR, 25 and 75%) were presented and the Mann-Whitney test was used. Overall survival in men and women was compared both for the whole population and for age subgroups (<70 years and ≥70 years) using the Kaplan-Meier method. Subsequently, survival curves were compared with the log rank test. Risk factors for the outcome, additional to sex, were assessed with the Cox proportion hazards model. First, significant preoperative variables additional to sex were compared with univariate Cox regression analysis. Thereafter, significant risk factors from the univariate analysis were included in a multivariable Cox regression analysis. Missing data (≤ 1.6%) were not included in the analysis. Patients lost to follow-up were not included in the Kaplan-Meier analysis and the Cox regression analysis as the date of loss to follow-up was unknown. Hazard ratios (HRs) are reported with 95% confidence intervals (CIs). Analyses of variance were used to compare the mean age of patients at the time of the operation as well as that at the time of death in case of mortality. For all tests, a p-value lower than 0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics 24 (SPSS Inc., Chicago, IL).

Results

Preoperative data

During a nineteen-year period, 2362 patients underwent isolated AVR in our department, 1322 (56%) of whom were men and 1040 (44%) were women. Data collection ended on July 1, 2017. The mean (± standard deviation (SD)) and median (interquartile range (IQR)) follow-up period of the survivors were 8.3 ±5.1 years and 7.8 years (3.9-12.3 years), respectively. Over

the entire study period, 36 patients (1.5%) were lost to follow-up. Baseline characteristics are listed in Table 1. Compared to men, women were older at the time of surgery (mean age of 69.9 ±10.6 versus 64.6 ±11.8 years, p < 0.001), and more of them had hypertension, were underweight (body mass index (BMI) < 20 kg/m2), obese (BMI > 30 kg/m2) and/or diabetic, they had lower hemoglobin levels and worse renal function. However, women had lower rates of chronic obstructive pulmonary disease (COPD), fewer women had left ventricular dysfunction, more presented with isolated aortic stenosis than men and fewer women had endocarditis.

Operative and postoperative data

Important operative and postoperative data of men and women are shown in Table 2. Compared to men, more women received biological valves rather than mechanical valves. In addition, the mean size of the implanted valves was smaller in women than in men. Red cell transfusions were performed more frequently in women than in men (55.9% versus 25.7%, p< 0.001), but fewer women received plasma and platelet transfusions. Also, re-explorations were performed significantly less frequently in women than in men (5.2% vs.

Table 1. Preoperative and demographic characteristics of patients undergoing isolated AVR

Variable	**Women** n=1,040	**Men** n=1,322	**p-value**
Age: years, mean ±SD	69.9 ±10.6	64.6 ±11.8	<0.001
Hypertension	511 (49.1%)	510 (38.6%)	<0.001
COPD	145 (13.9%)	241 (18.2%)	0.005
PVD	59 (5.7%)	91 (6.9%)	0.231
Prior CVA	45 (4.3%)	55 (4.2%)	0.842
Underweight (BMI <20 kg/m^2)	36 (3.5%)	24 (1.8%)	0.011
Obese (BMI >30 kg/m^2)	286 (28.0%)	237 (18.2%)	<0.001
Diabetes	161 (15.5%)	161 (12.2%)	0.020
LVEF<35%	18 (1.7%)	42 (3.2%)	0.027
Hemoglobin level: mmol/L, mean ±SD	8.1 ±0.7	8.8 ±0.9	<0.001
Renal function: ml/min/1.73m^2			<0.001
eGFR ≥60	543 (52.4%)	966 (73.4%)	
eGFR 30-60	471 (45.5%)	328 (24.9%)	
eGFR <30	22 (2.1%)	22 (1.7%)	
Aortic stenosis or insufficiency			<0.001
Stenosis	958 (92.1%)	1128 (85.3%)	
Combination	41 (3.9%)	65 (4.9%)	
Insufficiency	41 (3.9%)	129 (9.8%)	
Endocarditis	25 (2.4%)	83 (6.3%)	<0.001

Categorical variables are presented as percentages; continuous variables are presented as mean ± standard deviation or median (IQR); IQR: interquartile range (25-75%); SD: standard deviation. BMI: body mass index; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; eGFR: estimated glomerular filtration rate, calculated by using the MDRD (Modification of Diet in Renal Disease) formula (17); LVEF: left ventricular ejection fraction; PVD: peripheral vascular disease.

Table 2. Surgical and Postoperative Data of Patients Undergoing Isolated AVR

Variable	Women n=1,040	Men n=1,322	p-value
Surgical data			
Duration of ECC (min), median (IQR)	75 (62-91)	76 (63-92)	0.211
Aortic cross-clamp time (min), median (IQR)	55 (45-68)	57 (46-70)	0.082
Crystalloid cardioplegia (%)	862 (82.9%)	1,103 (83.4%)	0.334
Prosthesis type			< 0.001
Mechanical	336 (32.3%)	607 (45.9%)	
Biological	704 (67.7%)	715 (54.1%)	
Prosthesis size in mm, mean ± SD	22.1 ±1.6	24.6 ±1.9	<0.001
Postoperative data			
Re-exploration	54 (5.2%)	104 (7.9%)	0.010
Plasma transfusion	89 (8.6%)	161 (12.2%)	0.005
Number of units, median (IQR)	2.0 (2.0-4.0)	2.0 (2.0-4.0)	0.212
RBC transfusion	581 (55.9%)	340 (25.7%)	< 0.001
Number of units, median (IQR)	2.0 (1.0-3.0)	2.0 (2.0-4.0)	< 0.001
Platelet transfusion	45 (4.3%)	84 (6.4%)	0.031
Number of units, median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.448
CVA	9 (0.9%)	9 (0.7%)	0.609
TIA	5 (0.5%)	2 (0.2%)	0.252
Myocardial infarction	6 (0.6%)	10 (0.8%)	0.598
Early mortality (until d 30)	31 (3.0%)	29 (2.2%)	0.227

NOTE. Categorical variables are presented as percentages; continuous variables are presented as mean ± standard deviation or median (interquartile range). Abbreviations: AVR, aortic valve replacement; CVA, cerebrovascular accident; ECC, extracorporeal circulation; IQR, interquartile range; RBC, red blood cell; SD, standard deviation; TIA, transient ischemic attack.

7.9% respectively, p=0.010). Early mortality did not significantly differ between men and women (2.2% vs. 3.0% respectively, p=0.227).

Over the entire study period, 720 patients died (31.0%), 361 of whom were women and 359 were men. Overall mortality was 35.3% in women compared to 27.6% in men (p<0.001). The median survival was 18.5 years in men and 12.7 years in women. Compared to men, women had a worse 1-year survival (94.4% in women vs. 95.6% in men), 5-year survival (83.7% vs. 85.7%), 10-year survival (60.9% vs. 71.0%) and 15-year survival (40.7% vs. 58.0%) (figure 1 and table 3). Figure 2 presents the overall survival of patients in different age groups (below and over 70 years). Compared to men, the overall survival was significantly worse in women in the younger age group (76.9% in women vs. 81.3% in men; p=0.014). However, in the older age group of ≥ 70 years, there was no difference between men and women regarding survival (55.6% in women versus 57.9% in men; p=0.558). Table 4 shows the Cox

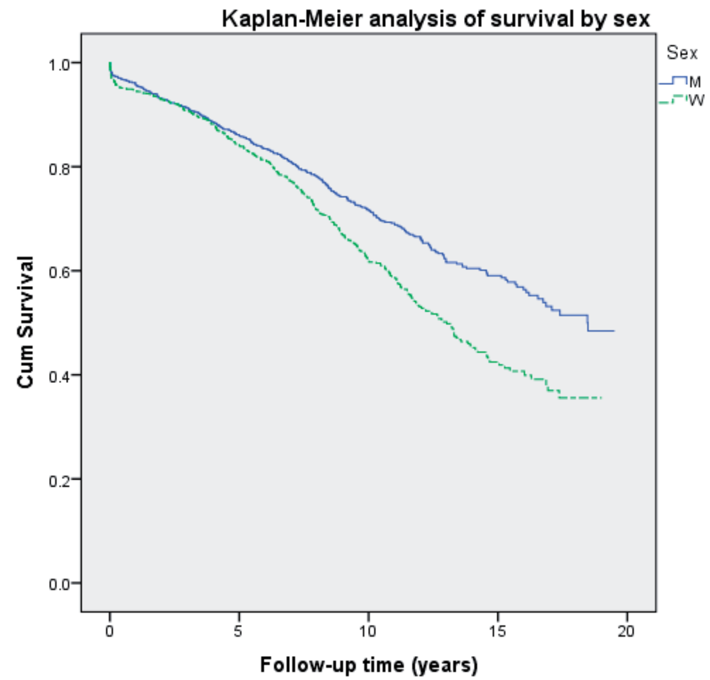

Figure 1. Kaplan-Meier analysis of survival bij sex

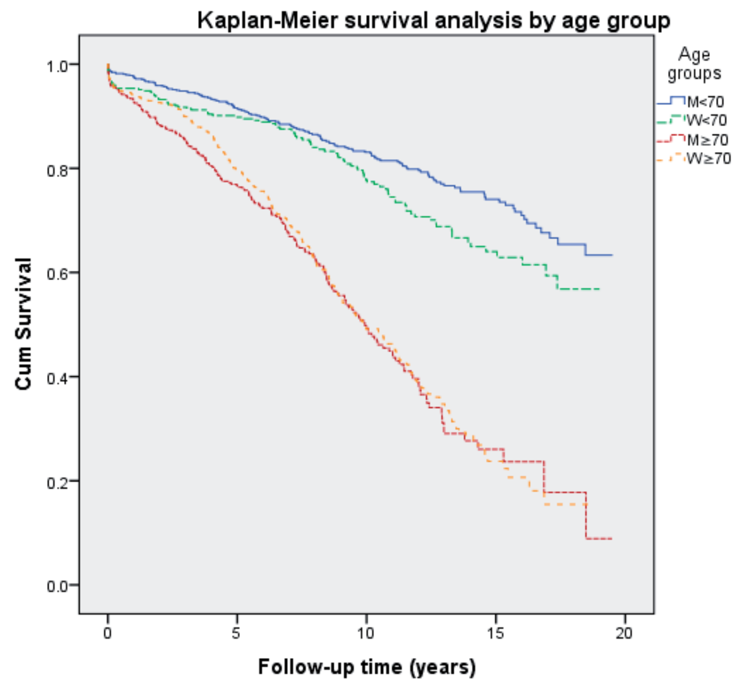

Figure 2. Kaplan-Meier survival analysis by age group

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Table 3. Kaplan Meier analysis of survival of patients undergoing isolated AVR

Variable	**Women** n=1,024	**Men** n=1,302	**p-value**
Survival time, median	12.698	18.456	<0.001
1-year survival: % (95% CI)	94.4 (93.0-95.8)	95.6 (94.4-96.8)	-
5-year survival: % (95% CI)	83.7 (81.3-86.1)	85.7 (83.7-87.7)	-
10-year survival: % (95% CI)	60.9 (57.2-64.6)	71.0 (68.1-73.9)	-
15-year survival: % (95% CI)	40.7 (35.8-45.6)	58.0 (54.1-61.9)	-

CI: confidence interval

proportional hazards model. Univariate Cox regression analysis identified sex as a risk factor for mortality. In the multivariable analysis, sex was not a significant predictor for overall survival. Factors that are significantly associated with poor survival in the multivariable model are age at the time of surgery, COPD, underweight, diabetes, left ventricular ejection fraction < 35%, preoperative hemoglobin and (expected glomerular filtration rate) eGFR <30 ml/min/1.73m2 (calculated with the Modification of Diet in Renal Disease formula 17). Figure 3A shows the mean age of men and women undergoing an AVR between 1998 and 2016. Both men and women underwent AVR at higher ages over time. Figure 3B presents the mean age of death of men and women in our population compared to the national statistics [16]. Over time, both men and women in our population were older at the time of death, as is also seen in the national statistics.

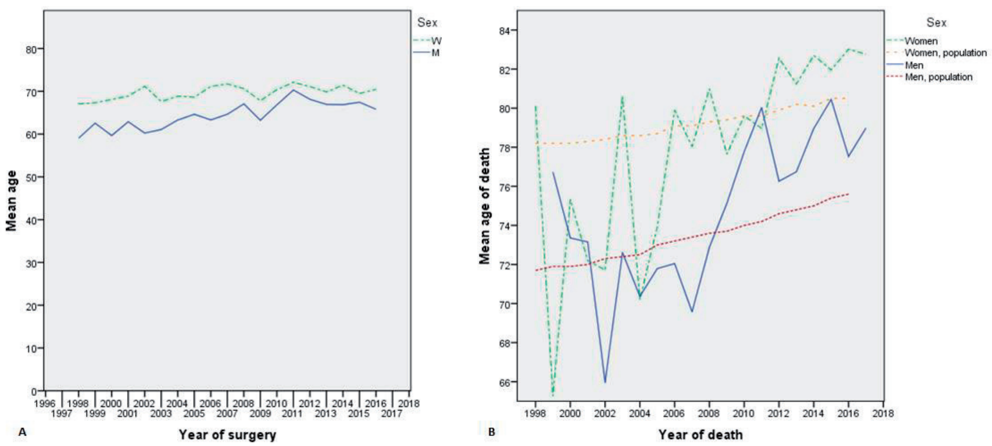

Figure 3. (A) Mean age of men (M) and women (W) undergoing aortic valve replacement surgery over time. (B) Mean age at the time of death in men and women after AVR compared to the Dutch Central Bureau of Statistics (CBS).

Table 4. Cox regression analysis for predictors/covariates of overall survival

Variable	**Univariable analysis**		**Multivariable analysis**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Gender	1.410 (1.218-1.632)	<0.001	0.923 (0.782-1.090)	0.347
Age: years	1.075 (1.065-1.084)	<0.001	1.072 (1.062-1.082)	<0.001
Hypertension	1.173 (1.009-1.364)	0.038	0.973 (0.832-1.139)	0.736
COPD	1.861 (1.573-2.203)	<0.001	1.785 (1.501-2.121)	<0.001
Underweight	1.732 (1.178-2.545)	0.005	2.207 (1.486-3.277)	<0.001
Obesity	0.991 (0.827-1.189)	0.926	-	-
Diabetes	1.675 (1.374-2.042)	<0.001	1.392 (1.133-1.710)	0.002
LVEF<35%	2.205 (1.544-3.149)	<0.001	1.687 (1.153-2.468)	0.007
Preop. Hemoglobin: mmol/L	0.749 (0.689-0.813)	<0.001	0.854 (0.778-0.938)	0.001
Renal function: ml/min/1.73m²				
eGFR ≥60 (reference)	1.00	-	1.00	-
eGFR 30-60	1.750 (1.496-2.046)	<0.001	1.151 (0.979-1.353)	0.088
eGFR <30	3.692 (2.505-5.442)	<0.001	1.813 (1.191-2.759)	0.006
Aortic insufficiency or stenosis				
Insufficiency (reference)	1.00	-	1.00	-
Combination	0.984 (0.726-1.334)	0.919		
Stenosis	0.575 (0.415-0.798)	0.001		
Endocarditis	0.739 (0.494-1.104)	0.139	-	-

Categorical variables are presented as percentages; continuous variables are presented as mean ± standard deviation or median (IQR); CI: confidence interval; HR: hazard ratio; IQR: interquartile range (25-75%); SD: standard deviation. COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction

Discussion

The aim of the present study was to establish whether female sex is one of the risk factors for unfavorable outcomes of AVR. We compared the patient profiles and outcomes of 1322 men and 1040 women who underwent isolated AVR in our hospital between January 1998 and December 2016. We found that women were older at the time of surgery and had a different preoperative risk profile than men. Despite the different pre-operative risk profile, early mortality did not differ significantly between men and women. Secondly, women had a higher overall mortality than men, but after risk adjustment this mortality was the same for both groups. Finally, the mean age at the time of death increased over the years in both sexes, which is in agreement with the general population. Women undergoing isolated AVR showed distinctly different pre-operative characteristics than men, which is in agreement with previous studies [1, 6, 10, 11, 18, 19]. Women undergoing AVR were more likely to suffer from isolated aortic valve stenosis than men, which was also seen in previous studies [19, 20]. This might have been due in part to the differences in the preoperative risk profiles of men and women [1]. Left ventricular function was better in women than in men. Differences in heart remodeling as a response to aortic stenosis may contribute to this finding as women develop more concentric hypertrophied hearts with less fibrosis. In contrast. men have a more eccentric pattern of hypertrophy with collagen deposition [9]. The finding that COPD was significantly less common in women than in men in our study population is interesting, as this is not in line with most previous studies. However, this finding is in agreement with the national Dutch COPD prevalence values [21], which might have been reflected in our population.

The finding that biological prostheses were used more commonly in women than in men is in concordance with the findings of some earlier studies [1, 3, 6, 10, 20, 22]. This can be explained by the age difference [23]. The mean implanted valve size was smaller in women, which was also observed in previous research [6, 10, 20, 22, 24]. Despite the different risk profile of women undergoing AVR, sex did not affect early mortality in our study. Previous studies showed mixed results. Caballero-Borrego et al [25] and Hamed et al [26] noted similar short-term mortality in men and women following AVR, after adjustment for baseline characteristics. Fuchs et al [6] and Saxena et al [10] both concluded that there is no difference between both sexes in either operative or long-term mortality after isolated AVR. According to Aranki et al [7], sex is not a predictor for operative mortality in the elderly after isolated AVR. However, in two recent studies, women had higher in-hospital mortality after AVR than men [1, 11]. In the present study, the relatively higher preoperative risk profile in women is balanced by the different pathophysiology of aortic valve disease and the indication of the operation, e.g. endocarditis. Men have a higher incidence of aortic insufficiency, with a higher incidence of impairment of the left ventricular function. In addition, the incidence of endocarditis in women is lower than in men, as was described previously [27]. Overall unadjusted mortality during the entire nineteen-year study period was higher in women than in men. Non-adjusted survival differed per age category (<70 and ≥70 years). This means that although women were relatively older than men at the time of surgery, the prognosis was worse when they presented at a younger age. After correction for baseline characteristics, there was no difference in overall mortality between men and women. This raises the important question whether women have a worse outcome after AVR merely because of female sex, or because of a higher incidence of preoperative risk factors. Previous studies that investigated long-term mortality in patients undergoing AVR yielded conflicting results [3, 6, 10, 28]. However, in those studies, the duration of follow-up was mostly limited. Kulik et al [3] reported a better long-term survival after bioprosthetic AVR (with or without CABG) in women compared to men in 3,118 patients with a mean follow-up period of 5.6 (±4.5) years. Fuchs and colleagues [6] found that long-term mortality was not increased in women in a population of 408 patients undergoing isolated AVR (mean follow-

up 3.6 ±2.2). In the oldest age group of patients aged 79 and older, women even showed better outcomes. An Australian study by Saxena et al [10], which included 2,790 patients who underwent isolated aortic valve replacement (up to 7 years follow-up) showed that women did not have an increased risk of late mortality. Elhmidi et al [28] showed that after adjustment, female sex was not associated with long-term mortality in 2,197 patients who participated in a prospective follow-up study that was conducted between 2000 and 2011. The present study suggests that women have a worse risk profile, which poses a greater risk of overall mortality. Female sex in itself, however, is not related with worse survival. The mean age of men and women undergoing AVR increased over the nineteen years of the study period, as was seen previously [29]. The mean age of death in our AVR population also increased over the years. This finding is in agreement with the increasing age of both sexes in the general population, a fact that should be considered before deciding to choose a suboptimal treatment for these patients.

Our study has some limitations. First, this is a retrospective study. However, with the relatively large patient population, various potential confounding factors were eliminated in the analysis. In addition, the primary end point of the study is all-cause mortality. We were not able to retrieve the cause of death, which might have been equally important.

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Conclusions

In our AVR population, women had a worse preoperative profile than men, but early mortality did not differ between the sexes. Overall survival was worse in women after AVR. However, after correction for pre-operative confounders, long-term survival was equal in both sexes and female sex was not an independent risk factor for overall mortality. When compared to the national Dutch population database, our population followed the national trend in that the age at the time of death increased during the study period.

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CHAPTER 6

Evolution of perioperative blood transfusion practice after coronary artery bypass grafting in the past two decades

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Abstract

Background & aim of the study: Transfusion of blood products after coronary artery bypass grafting (CABG) is associated with increased morbidity and mortality. We evaluated the perioperative usage of blood products in patients undergoing CABG in our institution over the past two decades.

Methods: The study included 18,992 patients who underwent isolated CABG at our hospital between 1998 and 2017. Baseline characteristics and the number of perioperative transfusions during hospital stay (including red blood cells [RBC], platelets and fresh frozen plasma [FFP]) were assessed. Logistic regression models were used to identify risk factors for perioperative transfusion.

Results: The rates of perioperative RBC transfusion decreased for all patients undergoing isolated CABG (52.1% in 1998 vs. 18.6% in 2017) in our institution. The mean number of transfused RBC units was significantly higher in females compared to males (1.57±2.2 vs. 0.68±1.84; $p<0.005$), this difference remained significant over the years. After adjusting the results for other risk factors, female sex was a significant independent factor for perioperative RBC transfusion. Platelet transfusion rate increased over the years (1.4% in 1998 vs. 9.7% in 2017). The number of FFP transfusions remained unchanged.

Conclusions: Over the past two decades, we observed a decrease in the incidence of perioperative RBC transfusions in patients undergoing isolated CABG, whereas platelet transfusions were increased. Female gender was an independent predictor for perioperative RBC transfusion.

Keywords: coronary artery bypass grafting, blood product transfusion, red blood cells, platelets, fresh frozen plasma.

Introduction

Transfusion of blood products in coronary artery bypass grafting (CABG) surgery is a common practice. The reported transfusion rates after CABG in the United States showed a wide variability between hospitals, ranging from 7.8% to 92.8% for red blood cells (RBC) with a mean of 56% [1]. Perioperative transfusion is known to be associated with increased short-term mortality and morbidity after CABG, including stroke, bacterial infections and prolonged hospital stay [2-5].

Considerable changes have occurred in CABG procedures over the last two decades. The patient population is getting older and the number of high-risk patients undergoing CABG is increasing [6,7]. Consequently, the risk of perioperative RBC transfusion is also increased. On the other hand, technical and procedural changes in addition to blood conservation programs have been developed [8-11]. One of the well-known risk factors of receiving perioperative blood transfusion after cardiac surgery remains the female sex [10]. In an earlier report, we described a program to minimize elective RBC transfusion in a selected group of patients undergoing cardiac surgery [12].

In the present study, we sought to evaluate the perioperative transfusion of the blood products including RBC, platelets and fresh frozen plasma (FFP) in patients undergoing isolated CABG procedures at our institution over the last two decades. Furthermore, we aimed to identify predictors for the need of perioperative blood transfusion focusing on the impact of sex.

Materials and Methods

In this retrospective study, data from all patients undergoing isolated CABG between January 1998 and July 2017 at our center were analyzed. Clinical data included demographic data and baseline risk factors including diabetes, left ventricular ejection fraction (LVEF), history of cerebrovascular accident (CVA), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), dialysis and prior cardiac surgery. Both operative data including the use of extracorporeal circulation and aortic cross-clamp time and postoperative results including blood product usage and the number of re-explorations for bleeding were prospectively collected in our database. This study conforms to the ethical guidelines of Helsinki and was approved by our institution's ethics committee with a waiver of informed consent.

Procedures

All procedures were performed through median sternotomy with normothermic extra-corporeal circulation (ECC), using non-pulsatile flow or an off-pump coronary artery grafting procedure (OPCAB). Activated coagulation time (ACT) was kept above the level of 440 seconds by the administration of heparin for patients undergoing CABG. In the case of an off-pump procedure, ACT was maintained at above 300 seconds. Cold crystalloid cardioplegia ('St Thomas' solution) or warm blood cardioplegia were used to induce and maintain cardioplegic arrest, according to the surgeon's preference. In 2002, we routinely started to use the cell saver in all CABG patients. At the end of the procedure, heparin was neutralized by protamine chloride. The dose of protamine was 1 mg per 1 mg of heparin administered. In 2008, a switch was made from aprotinin to aminocaproic acid as a standard anti-fibrinolytic drug during cardiac surgery procedures.

Study endpoints

The primary end point of this study was the incidence of perioperative transfusion of blood products, defined as transfusion during the procedure or within the first 5 days postoperatively. The database of our blood bank is linked to our electronic patient file; therefore, every blood product unit used during the hospital stay is immediately registered in the database.

In addition, the impact of sex as one of the most important predictors of perioperative blood transfusion was interesting. Therefore, the secondary end point of the study was the changes in blood transfusion incidences in both sexes. For this purpose, patient population was divided into two groups: males and females. In addition, we also collected the 120-day mortality every year of the study period to investigate the association between changes in blood transfusion practice and short-term outcome.

In our hospital, peri- and postoperative transfusion of one or more RBC units is indicated in patients with a hemoglobin (Hb) level of ≤ 5.0 mmol/L (80.6 g/L) or a hematocrit value of ≤22%. Hemoglobin levels of 6.0 mml/L (96.7 g/L) were adopted in cases of hemodynamically unstable patients or patients with postoperative ischemia. In the case of postoperative excessive bleeding, thromboelastography and standard coagulation tests were performed. Depending on the results, platelets or FFP were administered.

During the present analysis, we evaluated the usage of blood products such as RBC, FFP and platelets over the last two decades, represented as the mean number of units transfused per patient and displayed per year. In addition, we evaluated the number of patients receiving transfusion of one or more blood products. Demographic data, baseline risk factors, and perioperative and post-operative data, including blood product usage, were stratified by sex and addressed.

Statistical analyses

Discrete variables were compared with the x^2-test and are presented as numbers and percentages. The normality of distribution of continuous variables was tested by one-sample Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean (standard deviation [SD]). Means of 2 continuous normally distributed variables were compared by independent samples Student's t test. Univariate and multivariable logistic regression analyses were performed to investigate the impact of preoperative and perioperative factors on blood transfusion rates. Univariate analyses were used to test for the potentially confounding effect of biomedical and demographic factors on outcome. If significant at $p<0.05$, variables were included into the multivariable logistic regression model. A p value of <0.05 was used for all tests to indicate statistical significance. Odds Ratios with 95% confidence intervals are reported. All statistical analyses were performed using SPPS version 23.0 (SPSS Inc., Chicago, IL).

Results

From January 1998 to July 2017, 18,992 patients underwent isolated CABG procedure in our institution and were included in this study. Off-pump CABG (OPCAB) was performed in 3013 patients (15.9%) and 784 (4.1%) procedures were re-operations. The baseline characteristics of the total study population stratified by sex are shown in Table 1. The group of male patients was significantly younger than the group of female patients (64.6 ± 9.6 vs. 68.3 ± 9.4; p<0.001), showing a lower prevalence of diabetes (2962 (20%) vs. 1168 (27.8%); p<0.001)

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Table 1 Demographic characteristics

Variable	**Total** n=18,992	**Male** n=14,796	**Female** n=4,196	**p-value**
Age (years; Mean; SD)	65.4±9.7	64.6 ± 9.6	68.3 ± 9.4	<0.0001
Diabetes	4,130 (21.7%)	2,962 (20.0%)	1,168 (27.8%)	<0.0001
LVEF <35%	649 (3.4%)	521 (3.5%)	128 (3.1%)	0.139
History of CVA	820 (4.3%)	632 (4.3%)	188 (4.5%)	0.557
PVD	2,362 (12.4%)	1,834 (12.4%)	528 (12.6%)	0.744
COPD	2,048 (10.8%)	1,563 (10.6%)	485 (11.5%)	0.067
Dialysis	55 (0.3%)	41 (0.3%)	14 (0.3%)	0.547
Prior cardiac surgery	784 (4.1%)	638 (4.3%)	146 (3.5%)	0.017
Pre-op. CrCl (Mean; SD)	97.5 ± 43.2	100.4 ±42.8	87.0 ± 43.3	<0.0001
BMI Kg/m^2(Mean; SD)	27.4±3.9	27.3 ± 3.6	27.6 ± 4.7	<0.0001
Preop Hb, mmol/L; mean	8.7 ± 0.9	8.8 ± 0.9	8.0 ± 0.8	<0.0001

Data are represented as mean (±SD) or number (%).
LVEF–ejection fraction; CVA–Cerebrovascular accident; PVD–peripheral vascular disease; COPD–chronic obstructive pulmonary disease; Pre-op CrCl – pre-operative creatinine clearance; BMI – Body Mass Index; Pre-op Hb – preoperative haemoglobin.

and higher pre-operative hemoglobin and creatinine levels. The incidence of reoperations was significantly higher in the male group (638 (4.3%) vs. 146 (3.5%); p=0.017). There was no significant difference in the incidence of decreased left ventricular function, history of CVA, PVD, COPD or dialysis between the two groups.

Operative data

Extracorporeal circulation (ECC) time and aortic cross-clamp time was significantly longer in the male group (59 ± 36 min. vs. 57 ± 35 min.; p <0.001; 40 ± 24 min. vs. 37 ± 24 min.; p <0.001; respectively; Table 2). The number of patients undergoing an OPCAB procedure was significantly higher in the female group (719 (17.1%) vs. 2294 (15.5%); p=0.01). Re-exploration for bleeding was performed more often in the male group than in the female group (5.6% vs. 4.7%; p=0.03), while the incidence of perioperative myocardial infarction was lower in the male group than in the female group (2.6% vs. 3.3%; p=0.01).

Transfusion

A total of 5672 patients (30.0%) received one or more RBC transfusions peri-operatively. The number of patients receiving RBC transfusion decreased significantly over the past two decades (52.1% in 1998 to 18.6% in 2017, p<0.001; figure 1, figure 2). In contrast, the number of the perioperative platelet administration increased over the same period (1.4% in 1998 vs. 9.7% in 2017, figure 3). The rate of the FFP usage remained unchanged (8.5% in 1998 vs. 4.1% in 2017, figure 4). When stratified by sex, a significant difference in RBC transfusion rates is observed between the two sexes. The mean number of RBC unit transfusions is significantly higher in female patients than in male patients (Table 3 and figure 2). There is no significant difference between the two sexes regarding the mean number of platelet or plasma transfusions. However, the number of patients receiving either product is significantly higher in the male than female group (figures 3 and 4, Table 3).

Logistic regression analysis

Univariate logistic regression analyses revealed sex, age, reoperation, use of ECC, preoperative hemoglobin and creatinine level, body-mass index (BMI), PVD, history of CVA, decreased left ventricular function and COPD as significant factors associated with perioperative RBC

Table 2. Operative and post-operative data

Variable	**Total** n=18,992	**Male** n=14,796	**Female** n=4,196	p-value
ECC time (Mean; SD)	59 ±36	59 ± 36	57 ± 35	<0.0001
Aortic clamp time (Mean; SD)	39 ± 24	40 ± 24	37 ± 24	<0.0001
OPCAB	3,013 (15.9%)	2,294(15.5%)	719 (17.1%)	0.011
Re-exploration for bleeding	1,026 (5.4%)	828 (5.6%)	198 (4.7%)	0.026
Myocardial infarction	529 (2.8%)	391 (2.6%)	138 (3.3%)	0.014

ECC – extracorporeal circulation; OPCAB – off pump coronary artery bypass

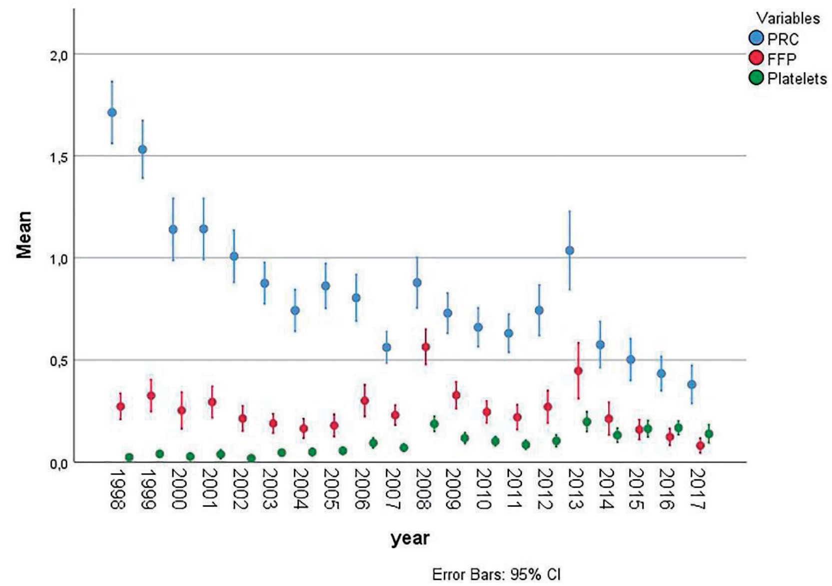

Figure 1. Mean number of perioperative received units of RBC, FFP and platelets over the last two decades.
RBC = Red Blood Cell
FFP= Fresh Frozen Plasma
Y-as: Mean number of transfused units

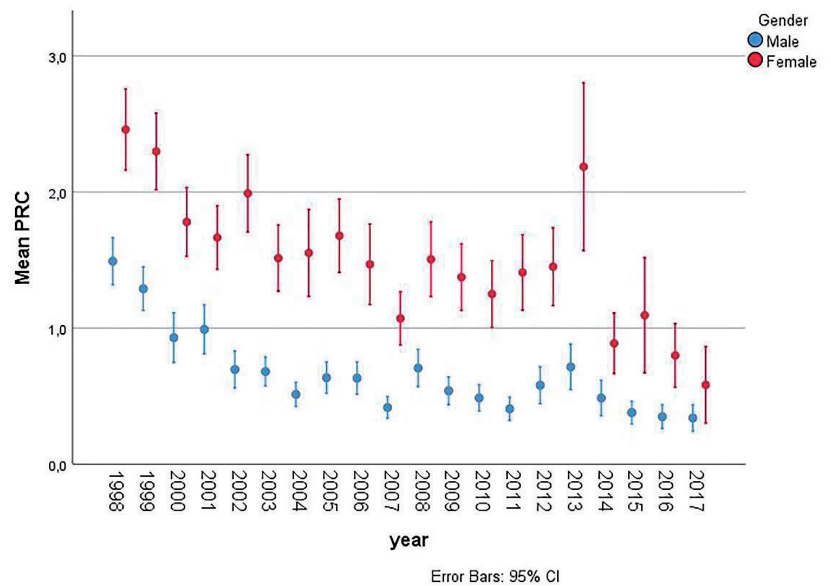

Figure 2. Mean number of perioperative received units of RBC over the last two decades, stratified by gender.
Y-as: Mean number of RBC units

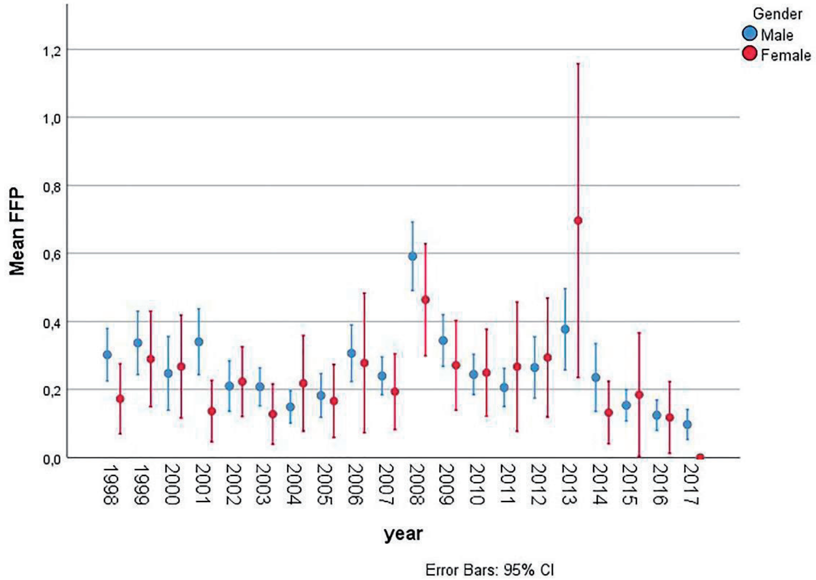

Figure 3. Mean number of perioperative received units of FFP over the last two decades, stratified by gender
Y-as: Mean number of FFP units

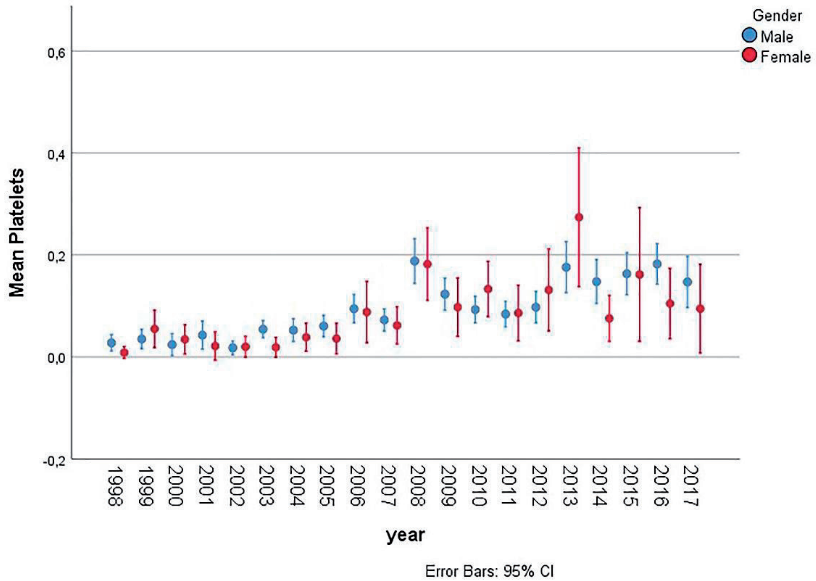

Figure 4. Mean number of perioperative received units of platelets over the last two decades, stratified by gender.
Y-as: Mean number of platelet units

Table 3. Rate of transfusion of blood products in both sexes.

Variable	Total n=18,992	Male n=14,796	Female n=4,196	p-value
Number of patients receiving RBC	5,672 (29.9%)	3,302 (22.3%)	2,370 (56.6%)	<0.005
Number of RBC units/ patient (Mean; SD)	0.88±1.96	0.68 ± 1.84	1.57 ± 2.20	<0.005
Number of patients receiving platelets	1107 (5.8%)	891 (6.0%)	216 (5.1%)	0.033
Number of platelet units/ patient (mean; SD)	0.09±0.40	0.09 ± 0.41	0.08 ± 0.40	0.153
Number of patients receiving FFP	1,598 (8.4%)	1,309 (8.8%)	289 (6.9%)	<0.005
Number of FFP units/ patient (mean; SD)	0.26±1.11	0.26 ± 1.10	0.24 ± 1.18	0.272

RBC –Red blood cell; FFP – fresh frozen plasma

Table 4. Logistic regression analyses for factors associated with perioperative red blood cell transfusions.

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Female Sex	4.52 (4.20-4.86)	0.0001	3.54 (3.23-3.88)	0.0001
Pre-op Hb	0.33 (0.32-0.35)	0.0001	0.41 (0.39-0.43)	0.0001
BMI	0.91 (0.91-0.92)	0.0001	0.91 (0.90-0.91)	0.0001
Pre-op. CrCl	1.01 (1.01-1.01)	0.0001	1.01 (1.01-1.01)	0.0001
Age	1.05 (1.04-1.05)	0.0001	1.01 (1.01-1.01)	0.0001
Reoperation	2.38 (2.07-2.75)	0.0001	3.25 (2.73-3.89)	0.0001
Use of ECC	2.44 (2.20-2.70)	0.0001	3.56 (3.14-4.04)	<0.0001
COPD	1.181 (1.07-1.30)	0.001	0.94 (0.84-1.06)	0.329
PVD	1.31 (1.19-1.43)	0.0001	0.92 (0.82-1.03)	0.129
Diabetes	1.26 (1.17-1.35)	0.0001	1.01 (0.92-1.11)	0.795
LVEF<35%	1.80 (1.54-2.11)	0.0001	1.41 (1.16-1.72)	0.001

Pre-op Hb – pre-operative haemoglobin; BMI – body mass index; Pre-op CrCl – pre-operative creatinine clearance; ECC–extracorporeal circulation; COPD–chronic obstructive pulmonary disease; PVD–peripheral vascular disease; LVEF–ejection fraction

transfusion (Table 4). These variables were entered into a multivariable logistic regression model. Female gender (OR 3.54 CI 3.23; 3.88; p<0.001), re-operation (OR 3.25 CI 2.73; 3.88 p≤0.001), lower BMI (OR 0.91 CI 0.90; 0.91 p≤0.001), lower pre-operative Hb (OR 0.41 CI 0.39; 0.43 p≤0.001), use of ECC (OR 3.56 CI 3.12; 4.04 p<0.001) and decreased left ventricular function (OR 1.41 CI 1.16; 1.72 p<0.001) were retrieved as independent risk factors for receiving RBC transfusion (Table 4).

Conclusions

The main finding of the present study is that the mean number of RBC unit transfusions in CABG patients has decreased over the last two decades. Previous studies in our center demonstrating complications with blood product transfusions have led to an awareness of physicians in order to avoid unnecessary blood product usage [13,14]. The results are clear; the number of patients receiving one or more perioperative RBC transfusions is also decreased. This is in line with other studies that also demonstrated a decreasing trend of RBC usage over time [15-17]. In the literature, transfusion rates of RBCs vary from 20% to 90% in patients undergoing isolated CABG [1,15,16, 18,19]. This wide variation can not only be explained by differences in patient characteristics or operative techniques. This difference is rather institution-dependent. There seems to be variation in indications and the availability of blood transfusion between different centers [1,16,20]. Moreover, adherence to guidelines and protocols concerning perioperative blood transfusion differs between centers and even between individual physicians [17].

In our institution, the transfusion of RBC is indicated in patients with a hemoglobin (Hb) level ≤ 5.0 mmol/L (80.6 g./L) or a hematocrit value of ≤22%. This policy has not been changed in the last two decades. The threshold hemoglobin level of 80.2 g/L adopted in our center is in accordance with the European guidelines of postoperative blood transfusion after cardiac surgery [21]. According to the European guidelines, two policies are adopted: restrictive (at Hb= 70.0-80.0 G/d) and liberal (at Hb= 90.0-100.0 g/L). A recent meta-analysis compared restrictive (Hb 70–80 g/L) and liberal (Hb 90– 100 g/L) transfusion strategies using data from 6 RCTs with 3352 patients, showing a 30% reduction in the number of deaths in the restrictive regimen group (OR 0.70, 95% CI 0.49–1.02; p=0.060) [22].

After the success of our NERC program [12], whereby the immediate availability of RBC units in the operating room is minimized, we successfully extended our criteria to include female sex, patients with a relatively lower BSA and patients undergoing isolated aortic valve replacements. In addition to patient benefits regarding mortality and morbidity, the program led to the more efficient transfusion policy in our center [12].

The risk profile of CABG patients regarding postoperative bleeding has changed in the last two decades. High numbers of patients are referred to surgery without discontinuing double oral antiplatelet therapy, which increases the risk of postoperative bleeding and transfusion [23]. However, we observed a decreasing incidence in the RBC transfusion and an increasing incidence of platelet transfusion over the last nineteen years. A possible explanation for this finding could be an earlier recognition of the compromised platelet function because of the increasing use of thromboelastography, leading to the earlier administration of platelets. Andreasen et al. [15] previously described the significant increase in the amount of platelet usage in CABG patients over the last years as a result of the development and early administration of new antiplatelet drugs. Our study confirms this finding, as we have observed a significant increase in platelet transfusion rates since 2008, when new generation antiplatelet drugs were introduced in our hospital, as described above. However, the association between the era of using of P2Y12 inhibitors and the relative increase in the transfusion of platelets should be further investigated. An important factor that could not be excluded is the personal attitude of the attending physician. Some physicians tend to give platelet transfusions sooner in patients with the preoperative use of P2Y12 inhibitors.

Despite an evident decreasing trend over the last two decades, the ratio of RBC transfusions between male and female patients remained the same. Moreover, female sex remained an independent predictor for receiving RBC transfusion in patients undergoing isolated coronary bypass grafting surgery. This finding remained unchanged and is in agreement with earlier investigations [10]. Furthermore, known risk factors of perioperative blood transfusion such as low body mass index, low preoperative HB, use of ECC and reoperation were confirmed in our study. This finding should be interpreted with caution, as women have a significantly lower preoperative hemoglobin level than men. In general, the preoperative risk profile of women is different than men. This contributes to a worse outcome, including the higher need for RBC transfusion in women. Considering the hemodilution effect of the priming volume of the ECC, a relatively considerable Hb drop could be expected in female patients. In multivariable analysis, female sex remained one of the predictors for receiving perioperative RBC transfusions after adjustment for all other risk factors. This finding was previously described by other authors [10,24,25] and investigated by Shevde et al. [26]. They suggested that female sex may interact with other factors determining the probability of transfusion, like age, weight, preoperative HB, and duration of surgery.

In our study, the impact of sex on the perioperative transfusion of other blood products, namely platelets and FFPs, needs some clarification. The mean number of transfused units of these products is not significantly different between the two sexes. However, the number of patients receiving these products is significantly higher in the male than female group. One possible explanation is that these products are often given in cases of re-exploration for bleeding. According to our results, the incidence of this complication is significantly higher in the male than female group.

This study has some limitations. First, this is a retrospective analysis that required data abstraction through electronic medical records; therefore, there are some missing data. However, data on the post-operative transfusion are complete due to direct links from the blood bank data to our database. Information regarding the discontinuation of antithrombotic and antiplatelet drugs before surgery, chest tube drainage, preoperative amounts of blood loss and amounts of blood washed out by cell savers are missing. Although our hospital has a definite policy regarding transfusion, we could not exclude the personal attitude of anesthetists or intensivists concerning the indication for transfusion.

In conclusion, we have observed a decreasing incidence of RBC transfusions after isolated CABG and an increase in the incidence of platelet transfusions in our institution over the past two decades, female sex remained an independent risk factor, among other factors associated with perioperative RBC transfusion.

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6

CHAPTER 7

7

General discussion

General discussion

In the past sixty years, cardiac surgery evolved into the general practice it is today. Fortunately, I was allowed to be part of the last thirty years and hopefully have been able to contribute to improve the level of cardiac surgery. Thanks to the database of the cardiothoracic surgery department of the Catharina hospital, we have been able to analyze the data of our patients to improve our cardiac surgery results. Recently, an increasing interest for women's cardiovascular health has led to a more sex- and gender-sensitive way to look at different risk factors for women [1]. Surprisingly, differences in outcome between men and women were examined in cardiac surgery since the start of coronary artery bypass grafting (CABG) [2,3]. The most important reason for investigating our patient population was to identify specific preoperative and postoperative risk factors for women and men. Finding an explanation for these differences, we might be able to provide women with appropriate and better decision-making and surgical treatment for their coronary artery and aortic valve disease. In this way, we can learn from the past and ensure that we do better in the future!

Coronary artery bypass grafting

The first coronary artery bypass surgery was performed in the United States on May 2nd., 1960, at the Albert Einstein College of Medicine-Bronx Municipal Hospital Center by Dr. Goetz and Dr. Rohman. The internal mammary artery was anastomosed to the right coronary artery [4]. The vessels were held together with circumferential ligatures over an inserted metal ring. In 1964, Dr. Kolesov, a Soviet cardiac surgeon, performed the first successful internal mammary artery for coronary artery bypass surgery using a standard suture technique [5]. In 1975, Al-Bassam et al [2] published the first article which addressed the differences between males and females in relation to the risk factors of atherosclerotic occlusive coronary artery disease in aorta coronary bypass (ACB). In that time (1969 until 1974), 13.2% of patients who underwent coronary artery bypass grafting (CABG) were female, they experienced 9.2% mortality. For men, mortality was 4.8%. They concluded that diabetes mellitus, hypertension, pre-infarction angina and recent myocardial infarction occurred more frequently in women. In that same year, Bolooki et al [3] concluded that although coronary artery disease shows anatomic similarity in women and men, the result of coronary revascularization in women is inferior to that in the male population (mortality 8.8% in women versus 2.0% in men). In 1984, Loop et al. [6] concluded that women had a higher operative mortality rate (2.9% versus 1.3%) in matched patients. Body surface area was the strongest predictor of operative risk, even when the model was adjusted for gender. Later in the century, Bukkapatnam et al. [7] evaluated a large cohort of women and men undergoing isolated CABG. Women (26.5% of total CABG) still had, approximately fifty years after the first CABG, higher mortality than men (4.60% versus 2.53%) despite adjustment for preoperative risk.

The EuroSCORE introduced by Dr. Nashef was the first scoring system for the prediction of early mortality in cardiac surgical patients in Europe on the basis of objective risk factors [8]. In this score, female gender had a 1% increase in mortality; later the 'female-risk-factor' was 0.3304052 in absolute percentage for mortality [9]. In our study on preoperative profile and early outcome (chapter 2), early mortality was also significantly higher in women than in men (2.7% versus 1.9%). Despite improved techniques for the extracorporal circulation (ECC), surgery, and pre- and postoperative care, the difference in operative mortality between women and men is still the same as it was a few decades ago. This could be explained by the fact that risk factors as age, hemoglobin level, creatinine level, hypertension, diabetes, chronic obstructive pulmonary disease (COPD) and peripheral vascular disease (PVD) have not become less prevalent in the last few decades. On the contrary, people become older, and women have 'emancipated' last decades in terms of socio-economics issues such as smoking. The fact that women have worse postoperative outcome after CABG, even in the last decades, could be explained by their older age at time of surgery. Furthermore, they suffer more from hypertension, diabetes, lower hemoglobin level, lower creatinine level, more weight disturbances such as underweight and obesity. Women experience a relative delayed in the onset of coronary artery disease, assuming that estrogen premenopausal has a protective effect on the coronary artery system. Despite this protective effect of estrogen, women in general have a more aggressive combination of factors (hypertension, diabetes, etc.) that influences surgical outcome after CABG.

The pathophysiology of coronary artery disease (CAD) is complex and still not completely understood. However, compared to men, women suffer more from coronary microvascular dysfunction (CMD) which could be the basis of premature coronary artery disease [10]. In approximately one half of women with chest pain, CMD is present even in de absence of obstructive CAD. Future research may provide more insight into the role of differences in pathophysiology between women and men.

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The early and 1-year mortality after CABG is significantly higher in women compared to men. They also have a worse overall long-term survival than men (chapter 3). This is probably due to the fact that women are older at time of surgery and that they have a higher risk profile. This worse survival of women can be calculated using the EuroSCORE, as the 'risk factor female sex' increases mortality percentage. The EuroSCORE only applies to early mortality, it cannot predict 1-year mortality or long-term survival. Early mortality will mainly be determined by issues related to heart surgery, long-term survival is the consequence of all-cause mortality on survival. In our study, we investigated large propensity matched groups (3,926 men and 3,926 women), all well-known risk factors (Hemoglobin, COPD, PVD, CVA, diabetes, low ejection fraction) were identified, as female gender was not. Therefore, the risk factor 'female gender' should be removed from the EuroSCORE for calculating surgical risk in patients undergoing CABG.

In our population, the long-term overall (non-adjusted) survival of women after CABG was also worse than men (Chapter3). After matching the two populations using propensity-score, no difference in long-term survival could be demonstrated. This finding is interesting but must be also cautiously interpreted. Using the same factors included in the EuroSCORE is validated for early mortality but not (yet) for long-term mortality. Moreover, our long-term data included all-cause mortality and not only cardiac mortality. We were not able to retrieve the cause of death which could be equally important. It is possible that other unknown factors or co-morbidities have affected the long-term survival other than the "EuroSCORE" factors. In a recent study including more than 26,000 Chinese patients [11], Wang et al found that age, and not female sex, is an independent predictor of long-term mortality after CABG. Further investigations with cardiac-related mortality as an end point are needed to verify the effect of gender on long-term mortality after CABG.

It is possible that the technical element of surgery plays an important role in the differences in outcome between the sexes. It is known that women have smaller and thinner coronary arteries than men, as reported by Rajakaruna et al. [12]. Diabetes is more common in women than in men, a finding that was confirmed by many other authors [12,13]. Obesity is also more common in women, which might contribute to the higher prevalence of diabetes in women. Being relatively smaller, diabetic target vessels are more challenging and difficult to graft, this could have a negative effect on graft patency and clinical outcome. It is well-known and that the mean number of performed grafts is fewer in women compared to men; this can also contribute to a worse outcome in women.

Normal surgical techniques for CABG involved the use of extracorporeal circulation (ECC) until the nineties. In 1995, Dr. Jansen started to use a specific beating heart method for coronary artery bypass grafting, using the Octopus [14,15], the so-called off pump coronary artery bypass grafting (OPCAB). This method was adapted all over the world in the years thereafter, as it was believed that OPCAB would have better patient outcome owing to avoiding the side effects of the extracorporal circulation (ECC). OPCAB surgery conserves the blood constituents, avoids global myocardial ischemia and may avoid neuropsychological deficits caused by malperfusion, micro emboli from CPB, and atheromatous emboli from manipulation of the aorta. Nuttall et al [16] demonstrated that not using ECC as in OPCAB surgery, reduces perioperative bleeding and is associated with an overall reduction of transfusion of blood products. In our study (chapter 4), we showed that, in both male and female populations undergoing CABG, a lower rate of blood transfusions and a higher postoperative level of hemoglobin was achieved after OPCAB compared to on-pump coronary artery bypass (ONCAB). This could be an important contribution to lower women's mortality in de OPCAB group than in de ONCAB group, as it is well-known that transfusion of red blood cells is an independent, dose-dependent risk factor for mortality after surgical revascularization [17].

During cardiopulmonary bypass, leukocyte contact with synthetic surfaces as in ECC, initiates a host defense reaction with the characteristics of a systemic inflammatory response syndrome (SIRS). Beside contact activation, ischemia-reperfusion injury, the reinfusion of shed blood, and hemodilution may contribute to the increased leukocyte adherence to vascular endothelium which also leads to a SIRS [18]. Beside the neurological effect on the brain by micro emboli during CPB and atheromatous emboli from manipulation of the aorta [19], the influence of apparently normal CPB procedures affect the impact of common clinical risk factors on postoperative neurologic complications. Patients who underwent CPB procedures with large fluctuations in hemodynamic parameters particularly showed an increased risk for the development of postoperative neurologic complications [20,21]. In our OPCAB female population, 120-day mortality is three folds higher in the ONCAB group than in the OPCAB group (3.6% versus 1.2%). This important finding suggests that women should preferably be operated for CAD using OPCAB surgery. Large, multicenter randomized controlled trials are needed to prove this might be true.

Aortic valve replacement

During the late 1940s and early 1950s, the first surgical approaches towards treating aortic valve stenosis (valvotomies) had limited success. The first operation was performed in October 1952 by Dr. Hufnagel. A ball valve prosthesis was placed in the descending thoracic aorta, resulting in patient survival for several years [22].

The first mechanical valve prosthesis was created and implanted by Dr. Star and Dr. Edwards in the US in 1960; the Star-Edwards valve. In that time, in-hospital mortality was 12.2% and late total mortality was as high as 26.5%. Complications were infection (patients received penicillin for 7 days postoperatively), post cardiotomy syndrome, psychosis, bleeding and heart block [23]. Tissue prosthetic valves were introduced in 1965 by Dr. Binet in Paris, but they degenerated quickly because the tissue was insufficiently preserved. Dr. Carpentier solved this problem by introducing glutaraldehyde-preserved stent-mounted porcine valves [24]. Later on, several types of biological valves became available, but the Carpentier-Edwards biological valve is still worldwide the most used biological aortic valve because of its durability [25]. Early mortality after aortic valve replacement (AVR) did not differ significantly between sexes in our population, 3.0% for women and 2.2% for men (chapter 5). Overall survival after AVR is worse for women than for men. Similar data were reported by other authors, though really long-term follow-up like in our study is sparse. Preoperative data in our group of patients showed that baseline characteristics differ between men and women. Women are older at time of surgery; this reflects the normal Dutch population [26] and is seen in other studies as well. Older age has an influence on postoperative complications and on in-hospital and long-term survival, but this applies for both women and men. Also, in the AVR population, women have relatively more risk factors than men; hypertension, underweight, obesity, diabetes, lower hemoglobin level and worse renal function. These findings can explain why women have a higher mortality after AVR compared to men. After risk adjustment, there was no difference in mortality between the two groups. Surgical data of this study showed that more women received a biological valve (67.6% versus 54.1%) than men, and that the mean size of implants is smaller in women compared to men (22.1mm versus 24.6mm). Survival after aortic valve replacement appears not to be affected by patient-prosthesis mismatch [27]. If there is a strong mismatch, aortic root enlargement to accommodate a large prosthesis is considered. Women are smaller than men and are older at age of surgery. Dr. van Geldorp found that even for patients aged 60, event-free (risk of bleeding) life expectancy is better with a bioprosthetic compared to mechanical valves [28].

The EuroSCORE is a statistical model which calculates perioperative mortality in patients undergoing cardiac surgery. It was originally designed by Dr. Nashef in the nineties of the last century for CABG populations. In this model, female gender is an important risk factor [8]. In our AVR population study, after correction for preoperative risk factors, female gender is not a risk factor for early mortality. Therefor, the EuroSCORE is not the best instrument to calculate mortality in AVR patients and sex might be deleted as a risk factor from the EuroSCORE.

An interesting, and becoming more and more popular technique is Transcatheter Aortic Valve Implantation (TAVI). The first TAVI was performed bij Dr. Cribier on April 16th. 2002 at the Charles Nicolle University Hospital in Rouen, France [29]. The initial purpose of this technique was to help patients who were inoperable due to their age or co-morbidity, often expressed in a high EuroSCORE. At the beginning, peri-procedural mortality was high but in time, mortality rate decreased to 2.2% for men versus 2.6% for women [30]. Other important determinants of outcomes after TAVI are the postoperative presence of residual aortic regurgitation (AR) and the need for permanent pacemaker implantation. The incidence of post-procedural AR grade ≥2 (where grade 2 is mild) is 20.9% in women and 29.6% in men. This finding could be explained by the fact that women have a smaller annulus and higher cover index for the prosthesis. In surgical AVR (SAVR) the incidence of postoperative paravalvular leakage (PVL) is low, van Nooten et al. reported only 0.33% per patient year [31]. A recent study from Matteucci et al. showed that after SAVR, at hospital discharge, aortic PVL was present in 11.7% while the majority (78.3%) of the PVLs was mild. Further analysis identified female sex as one of the predictors of early aortic PVL [32].

Another major problem of TAVI technique is the peri-operative total atrioventricular block In the study of Laricchia et al., the incidence was 9.6% in women versus 17.2% for men [30]. One suggested explanation for the higher incidence of permanent pacemaker (PPM) implantation in men as compared to women is the use of larger prostheses. In the study of Matthews et al, the incidence of PPM implantation following SAVR varied from 3.0% to 11.8% (mean 7.0%) [33]. Poels et al. showed that persistent postoperative left bundle branch block (LBBB) and right bundle branch block (RBBB) occur relatively infrequently (4.0% and 5.2%), a percentage more than half of that in current TAVI procedures [34]. Patients with RBBB and LBBB had higher risk of overall mortality. Women with RBBB had more risk of all-cause death than men while LBBB was associated with higher risk of cardiovascular mortality [35]. Given these adverse effects of LBBB and RBBB, the lower prevalence of procedure-induced LBBB and RBBB and the lower incidence of PVL in SAVR, should be taken into account while deciding which valve replacement procedure is chosen for each patient. Despite the complications of TAVI, techniques will evolute towards better results and in future this technique can possibly be used in larger groups of (female) patients. Until then, SAVR will remain the technique of choice for low and medium risk patients.

Perioperative blood transfusion

As early as in 1628, the English physician Dr. Harvey discovered the circulation of blood and shortly afterwards, the earliest known blood transfusion was attempted. The first successful transfusion of human blood for the treatment of postpartum hemorrhage was performed by the British obstetrician Dr. Blundell in 1811. Dr. Landsteiner, an Austrian physician, discovered in 1900 the first three human blood groups, A, B, and C. Blood type C was later changed to O. His colleagues Dr. Decastello and Dr. Sturli added AB, the fourth type, in 1902. Landsteiner received the Nobel Prize for Medicine for this discovery in 1930. When open heart surgery started in 1950, blood use entered its most explosive growth period. Nowadays, adult cardiac surgery accounts for a significant proportion of all red blood cell (RBC) transfusions all over the world [36, 37]. In patients undergoing coronary artery bypass grafting (CABG), transfusion of RBC and other blood products is not only associated with increased mortality and morbidity, but also with a longer intensive care unit (ICU) stay, increased infection and a total hospital stay [38]. Each unit of red cells transfused is associated with an incrementally increased risk for adverse outcome. Koch et al. claimed that perioperative RBC transfusion is the single factor most reliably associated with increased risk of postoperative mortality after CABG [39]. In our institution, the mean number of RBC unit transfusions in CABG patients has decreased during the last twenty years from 52.1% in 1998 to 18.6% in 2017 (chapter 6). This is probably the result of more awareness of physicians of the dangers of RBC transfusion and the introduction of a new protocol in 2010 which led to reduced RBC consumption [40]. The mean number of RBC was significantly higher in women than in man, This difference remained unchanged over twenty years. Dr. van Straten found that female gender is a predictive factor for transfusion of RBC after CABG [41]. This is in agreement with other studies; Shevde et al. claimed that gender is an independent essential determinant of blood transfusion in CABG patients [42]. In general, the preoperative risk profile for women is different from men at time of surgery; women are older, they have higher prevalence of diabetes, lower creatinine levels and lower hemoglobin (Hb) levels than men. In our institution, the policy of RBC transfusion is guided by a Hb level ≤5mmol/L (80.6 g/L) or a hematocrit value ≤22%. This policy did not change in the last twenty years and is in accordance with the European guidelines of postoperative blood transfusion after cardiac surgery [43]. This could be an explanation why women are receiving more RBC after CABG compared to men. Most females have lower body surface area (BSA) due to smaller body size and therefore smaller circulating volume and with the use of extracorporal circulation (ECC), hemodilution is proportionally greater for women than for men. This results in lower Hb after CABG and more transfusion of RBC. However, in our study, the number of women undergoing off-pump coronary bypass grafting (OPCAB) was significantly higher compared to men. Nuttall et al. showed that OPCAB surgery is associated with an overall reduction in RBC transfusion requirements [16]. In our study, use of ECC was retrieved as independent risk factor for receiving RBC transfusion. This was also seen in our study described in chapter 4.

Platelet transfusion rate increased over the years, 1.4% in 1998 versus 9.7% in 2017, whereas the number of fresh frozen plasma (FFP) remained unchanged. We also observed a change in risk profile for postoperative bleeding in patients undergoing CABG. Firanescu et al. showed that continuation of clopidogrel until the day of surgery induces significantly more postoperative blood loss and increases significantly the total requirements of homologous blood products and FFP transfusion after surgery [44]. The benefit of dual antiplatelet therapy (DAPT), such as clopidogrel combined with aspirin, is well-established in the treatment of acute coronary syndrome. Aspirin maintenance during surgery does not increase the postoperative bleeding in CABG patients, but after continuation of DAPT until CABG, postoperative bleeding at 24 hours increased by 22%, compared with the aspirin group [45]. Tomsic et al. showed, in their recent study, that ticagrelor discontinuation >72 hours prior to surgery and clopidogrel discontinuation >120 hours prior to surgery were not associated with an increased occurrence of bleeding-related complications in patients undergoing isolated on-pump CABG. Ticagrelor appears to be a safe alternative to clopidogrel in patients requiring DAPT prior to CABG whereby a shorter washout period is sufficient to avoid significant bleeding-related complications [46]. In conclusion, there is a decrease in the incidence of perioperative RBC transfusions in patients undergoing isolated CABG, not only in our institution but also worldwide. However, platelet transfusions are still increasing due to new oral antiplatelet double or triple therapy, and this should be further investigated.

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CHAPTER 8

Summary and conclusions

Cardiovascular disease is the leading cause of mortality in women, they represent a growing population of patients undergoing cardiac surgery. It is important to understand the factors contributing to the higher mortality in the female population after cardiac surgery. The last decade there is a growing awareness which factors contributes to the pathophysiology of cardiovascular disease in women.

Chapter 1

An overview of previous reports in literature concerning cardiac surgery in female patients compared to male patients is described in this chapter. The different preoperative risk profile for women, as displayed in the EuroSCORE and the STS score, is explored in regard to coronary artery bypass grafting and aortic valve replacement. Transfusion of blood products is associated with increased morbidity and mortality, the different impact on either sexes is still unclear and is still being investigated. The objectives of this thesis are described.

Chapter 2

This chapter describes the preoperative risk factors for men and women in a large retrospective study for coronary artery bypass grafting (CABG). In this study we showed that women were older, had a lower hemoglobin level, a lower creatinine level, more often hypertension, diabetes, underweight and obesity compared to men. The mean number of grafts was less in women but the mean cross-clamp time per graft was longer, probably due to smaller coronary artery vessels and more severe atherosclerosis. Logistic regression analyses showed that chronic obstructive pulmonary disease, peripheral vascular disease, cross-clamp time and underweight were independent risk factors for early mortality only in men. We conclude that the predictive value of well-known risk factors for early mortality after CABG is different between the two sexes.

Chapter 3

The long-term outcomes and the patient profiles comparison between men and women undergoing isolated coronary artery bypass grafting (CABG) is described in this chapter. We performed a multivariate logistic regression and a large propensity score-matched analysis (3,926 man and 3,926 women), the mean follow-up was 9.6 ± 4.9 years. Women were older and had lower hemoglobin levels preoperatively, early mortality (30-day) and 1-year mortality was significantly higher in women compared to men (1.8% vs. 2.8%; $p<0.001$ and 3.8% vs. 5.2%; $p<0.001$). They also had a worse overall long-term survival (5, 10, 15-year men versus women 10.6% vs. 12.3% $p=0.003$, 19.9% vs. 24.2% $p<0.001$, 25.7% vs. 32% $p<0.001$). The propensity score-matched analysis revealed that female sex was not an independent risk factor for long-term mortality.

Chapter 4

There is a considerable controversy between different studies concerning the advantage of off-pump coronary artery bypass grafting (OPCAB) compared to on-pump coronary artery bypass grafting (ONCAB), especially in women. The data of both groups (OPCAB and ONCAB) were analyzed and showed that mean number of grafts was less in de OPCAB group for both genders but patients received fewer red blood cell transfusions and had higher hemoglobin postoperative. Early mortality was lower in the OPCAB group for men and women, although the difference was not significant. The 120-day mortality was significantly lower for women in the OPCAB group (mortality OPCAB vs ONCAB 1.2% vs 3.6%), even after correction for preoperative risk factors (odds ratio=0.356, 95% confidence interval 0.144-0.882, $p=0.026$), but not for men.

Chapter 5

This chapter deals with comparison of patients' profiles and outcomes of men and women undergoing isolated aortic valve replacement. This study showed that women were older (69.9 years vs 64.6 years $p<0.001$), and had more risk factors like underweight, obesity, diabetes, lower hemoglobin, worse renal function compared to men. However less women suffered from chronic obstructive pulmonary disease, aortic regurgitation, left ventricular dysfunction and endocarditis than men. Early mortality did not significantly differ between men and women ($p=0.238$) but overall survival was worse in women ($p<0.001$) and after correction for potential risk factors, female gender was not associated with worse survival. In this study period, the mean age of our patients undergoing aortic valve replacement increased, also the mean age at time of surgery, following the trend of national statistics.

Chapter 6

The evaluation of the perioperative usage of blood products in patients undergoing coronary artery bypass grafting (CABG) in the Catharina Hospital over the last decades is described in this chapter. Transfusion of blood products after CABG is associated with increased morbidity and mortality. Between 1998 and 2017 we included 18,992 patients who underwent isolated CABG in our institution, the rates of perioperative red blood cell

(RBC) transfusion in isolated CABG decreased during time; 52.1% in 1998 versus 18.6% in 2017. The mean number of transfused RBC units was significantly higher in the female group compared to males (1.57±2.2 versus 0.68±1.84; $p<0.005$), this difference remained significant throughout the 20 years. Female sex was a significant independent factor for perioperative RBC transfusion after adjusting the results for other risk factors. Platelet transfusion rate increased over the years (1.4% in 1998 versus 9.7% in 2017) possibly due to the increased use of new generation antiplatelet drugs (P2Y12 inhibitors).

Chapter 7

The main findings of the thesis are discussed and compared with the results with recent studies in the literature.

CHAPTER 9

9

Nederlandse samenvatting

De belangrijkste doodsoorzaak bij vrouwen is tegenwoordig hart- en vaatziekten, zij vertegenwoordigen een groeiende groep patiënten die een hartoperatie moeten ondergaan. Omdat vrouwen na een hartoperatie een hogere morbiditeit en mortaliteit hebben, is het belangrijk proberen te begrijpen welke factoren daartoe bijdragen. De laatste 10 jaar is er een betere bewustwording van deze toename van hart- en vaatziekten bij vrouwen, hierdoor wordt er veel onderzoek gedaan naar de pathofysiologie hiervan bij vrouwen.

Hoofdstuk 1

In dit hoofdstuk wordt een overzicht gegeven van de literatuur van de hartchirurgie en de verschillen in uitkomsten tussen mannen en vrouwen. De verschillende preoperatieve risicoprofielen voor vrouwen worden weergegeven in de EuroSCORE of de STS-score, deze wordt onderzocht in relatie tot coronary artery bypass grafting en aortaklep vervanging. Het toedienen van bloedproducten perioperatief gaat gepaard met een verhoogde morbiditeit en mortaliteit, wat dit voor de beide geslachten betekent is nog niet duidelijk en dient verder onderzocht te worden. De onderzoeksvragen van deze thesis worden beschreven.

Hoofdstuk 2

Een grote retrospectieve studie naar perioperatieve risicofactoren van mannen en vrouwen bij coronary artery bypass grafting (CABG) wordt in dit hoofdstuk beschreven. Hierin wordt aangetoond dat dat vrouwen ouder zijn, een lager hemoglobine, een lager creatinine gehalte, vaker hypertensie, diabetes, ondergewicht en overgewicht hebben in vergelijking tot mannen. Bij vrouwen is het gemiddeld aantal grafts minder maar de x-klem tijd langer, dit zou mogelijk het gevolg kunnen zijn van het feit dat de kransslagaders bij vrouwen kleiner zijn en meer atherosclerose hebben in vergelijking tot mannen. Logistische regressieanalyse laat zien dat chronische obstructive pulmonary disease, perifeer arterieel vaatlijden, x-klemtijd en ondergewicht onafhankelijke risico factoren zijn voor vroege mortaliteit bij mannen. Wij concluderen dan ook dat de voorspellende waarde van de bekende risico factoren voor vroege mortaliteit na een CABG verschillend is voor beide geslachten.

Hoofdstuk 3

In dit hoofdstuk wordt een onderzoek beschreven waarbij de lange termijn resultaten van CABG worden bekeken en de patiënten profielen van mannen versus vrouwen vergeleken. Daarvoor werd een multivariate logistische regressieanalyse en een grote propensity matched analyse (3.926 mannen versus 3.926 vrouwen) verricht, de gemiddelde follow up was 9,6 ± 4,9 jaar. Preoperatief waren vrouwen ouder en hadden een lager hemoglobine gehalte, de vroege mortaliteit (30 dagen) en 1 jaar mortaliteit was significant hoger bij vrouwen vergeleken met mannen (1.8% versus 2.8%; $p<0.001$ en 3.8% versus 5.2%; $p<0.001$) en was er ook een slechtere overall lange termijn overleving (5, 10, 15 jaar mannen versus vrouwen 10.6% vs. 12.3% $p=0.003$, 19.9% vs. 24.2% $p<0.001$, 25.7% vs. 32% $p<0.001$). Bij de propensity matched analyse was het vrouwelijke geslacht geen onafhankelijke risico factor voor lange termijn mortaliteit.

Hoofdstuk 4

Er bestaat geen consensus in de diverse studies die gekeken hebben naar het voordeel van off-pump coronary artery bypass grafting (OPCAB) in vergelijking met on-pump coronary artery bypass grafting (ONCAB), vooral als gekeken wordt naar vrouwen. De data van beide groepen patiënten (OPCAB en ONCAB) werden geanalyseerd en laat zien dat het aantal grafts per patiënt in de OPCAB-groep lager is voor beide geslachten. Patiënten die een OPCAB-operatie ondergaan kregen minder rode bloedcel transfusies en hadden een hoger hemoglobine postoperatief. De vroege mortaliteit was lager in de OPCAB-groep bij zowel mannen als vrouwen ofschoon dit niet statistisch significant was. De 120-mortaliteit was significant lager bij vrouwen in de OPCAB-groep (mortaliteit OPCAB versus ONCAB 1,2% vs. 3,6%), zelfs na correctie voor de preoperatieve risico factoren (odds ratio=0.356, 95% confidence interval 0.144-0.882, $p=0.026$), dit was bij mannen niet het geval.

Hoofdstuk 5

Dit hoofdstuk gaat over mannen en vrouwen die een aortaklep vervanging hebben ondergaan waarbij de patiënten profielen en resultaten worden vergeleken tussen beide groepen. Deze studie toont aan dat vrouwen ouder zijn dan mannen ten tijde van de operatie (69,9 jaar versus 64,6 jaar $p<0,001$). Ze hadden ook meer risico factoren zoals ondergewicht, obesitas, diabetes, lager hemoglobinegehalte en een slechtere nierfunctie in vergelijking met mannen. Minder vrouwen hadden chronic obstructive pulmonary disease , aortaklep insufficiëntie, verminderde linker kamer functie en endocarditis in vergelijking met mannen. De vroege mortaliteit verschilde niet tussen mannen en vrouwen ($p=0,238$) maar de overall overleving was slechter bij vrouwen ($p<0.001$). Na correctie voor potentiele risico factoren was het vrouwelijke geslacht niet geassocieerd met een slechtere overleving. Tijdens de studieperiode nam de leeftijd van alle patiënten die een aortaklep vervanging ondergingen toe, dit is dezelfde trend die terug te vinden is bij de Nederlandse bevolking.

Hoofdstuk 6

In dit hoofdstuk wordt de evaluatie van het gebruik van bloedproducten van patiënten die een coronary artery bypass grafting (CABG) in het Catharina ziekenhuis hebben ondergaan gedurende de laatste decennia beschreven. Het transfunderen van bloed na een CABG wordt geassocieerd met een verhoogde kans op morbiditeit en mortaliteit. Tussen 1998 en 2017 ondergingen 18.992 patiënten een geïsoleerde CABG-operatie in het Catharina ziekenhuis, het aantal rode bloedcel (RBC) transfusies daalde in de loop van de jaren; 52,1% in 1998 versus 18,6% in 2017. Het gemiddelde aantal getransfundeerde RBC eenheden was significant hoger bij vrouwen dan bij mannen (1.57±2.2 versus 0.68±1.84; $p<0.005$), dit verschil bleef significant constant gedurende 20 jaar. Het vrouwelijke geslacht was een significant onafhankelijke factor voor het krijgen van RBC-transfusie ook na aanpassing van de resultaten voor andere risicofactoren. De transfusie van bloedplaatjes is toegenomen in de loop der jaren (1,4% in 1998 versus 9,7% in 2017), dit is waarschijnlijk het gevolg van het toegenomen gebruik van nieuwe generaties bloedverdunners (zogenaamde P2Y12 inhibitoren).

Hoofdstuk 7

De belangrijkste bevindingen van het proefschrift worden besproken en vergeleken met de resultaten van recente studies in de literatuur.

9

CHAPTER 10

10

Valorisation
Curriculum vitae
List of publications
Dankwoord

Valorisation

Cardiovascular disease (CVD) is the leading cause of mortality for women in Europe (49% in women and 40% in men). There is still an ongoing misperception that women under the age of 65 years are at low risk for CVD. Even medical practitioners are prone to the misconception of CVD being a predominantly male problem. Women undergoing coronary artery bypass grafting (CABG) have a different perioperative risk profile compared to men and their postoperative outcome is worse. It is still not completely understood which factors contribute to women having a worse outcome compared to men. Both in the EuroSCORE as well as in the STS score who are used to estimate the risk of perioperative mortality in cardiac surgery, the 'risk factor' female gender gives a higher change of mortality compared to male gender.

It was our main goal to study perioperative risk factors in relation to the 'risk factor' female gender. The department of cardiac thoracic surgery of the Catharina Hospital has an extensive database which has been maintained from 1998 until now. That is why we can conduct extensive research into large groups of patients and draw statistically significant conclusions.

The first study we performed is described in Chapter 2: a large cohort of patients (13,903 men and 4,016 women) was studied. The main finding was the considerable difference in preoperative profile between male and female populations undergoing CABG. Women were older than men at the time of CABG and had greater number of preoperative comorbidities, including hypertension, diabetes, obesity, and anemia. Probably, women experience a delayed onset of cardiac disease, compared to men, until the onset of menopause, presumably because of the protective effects of estrogen on the cardiovascular system. The incidence of early mortality was significantly higher in women than in men (2.7% versus 1.9% $p=0.001$) and the predictive value of well-known risk factors for early mortality was different between the 2 sexes. Chronic obstructive pulmonary disease (COPD), peripheral vessel disease (PVD) and underweight were identified as independent risk factors for early mortality only in men. These findings must be considered when stratifying the risk for CABG patients.

Differences between men and women in long term outcome, mean follow-up period was 9.6 ± 4.9 years, after CABG is described in Chapter 3. Here we reviewed all consecutive patients (total 17,663) undergoing CABG and after statistical analysis early mortality and 1-year mortality were significantly higher in women compared to men. Also, women showed a worse overall long-term survival than men. Multivariate analysis revealed female sex, age, hypertension, diabetes, PVD, COPD, prior cerebral vascular accident (CVA), left ventricular dysfunction as significantly associated with higher long-term mortality. We also performed propensity score-matched analyses (3,926 man and 3,926 women) and analyzed the independent risk factors for short-, medium- and long-term mortality. The main conclusion of the outcome of this propensity matched group was that female sex was not an independent risk factor for long-term mortality. It seems logical that independent risk factors, and not female gender, predicts the outcome in survival after CABG. Therefor female gender must be excluded as a risk factor for long-term mortality.

Off pump coronary artery bypass grafting (OPCAB), used for the first time in de nineties, is still a well-established technique for treatment of CVD. Several authors reported about the advantages and disadvantages of OPCAB since this technique was introduced. There are some studies which showed that women might have better survival after OPCAB surgery compared to on-pump coronary artery bypass grafting (ONCAB). In Chapter 4 we compared two groups of patients in outcome after CABG, OPCAB versus ONCAB. The 120-days mortality showed that de OPCAB female group has three times lower mortality than the ONCAB female group (1.2% versus 3.6%). This is an important finding, OPCAB surgery is the preferential treatment for women suffering from CVD.

Aortic valve replacement (AVR) is a common surgical procedure in our cardiac thoracic surgery practice. As people become older, there is a growing population of patients undergoing AVR. In Chapter 5 we compared patient profiles and outcomes of men and women undergoing isolated aortic valve replacement. In a nineteen year period we evaluated 2362 patients, 1040 (44%) of whom were women and 1322 were men (56%). Although women have relatively more risk factors than men, like older age (69.9 years vs. 64.6 years, $p<0.001$), more underweight, obese and diabetic. They also had lower hemoglobin and worse renal function than men but less women suffered from chronic obstructive pulmonary disease, aortic regurgitation, left ventricular dysfunction and endocarditis than men. Early mortality in women was not significantly higher than in men, but the overall survival was worse in women than in men. After adjustment for preoperative risk factors, there is no difference in overall survival between women and men. The estimated mortality risk score, used by cardiologists and cardiac surgeons, is the EuroSCORE where female gender is a predictor of higher mortality. In our study the risk factor 'female gender' had no influence on the overall survival in patients undergoing AVR, this should be further investigated.

Unfortunately transfusion of blood products after CABG is associated with increased morbidity and mortality. Because we have built up a large detailed database over the last 20 years, it was possible to study the results of a large cohort of patients undergoing CABG and the use of blood products in relation to mortality, as discussed in Chapter 6. We included 18,992 patients who underwent isolated CABG, between 1998 and 2017. In time, the rates of perioperative RBC transfusion decreased for all patients undergoing isolated CABG (52.1% in 1998 versus 18.6% in 2017). The mean number of transfused RBC units was significantly higher in females compared to males (1.57±2.2 versus 0.68±1.84 ; p<0.005) and after adjusting the results for other risk factors, female sex was a significant independent factor for perioperative RBC transfusion. If we can change the guidelines for prescribing RBC, not only the costs associated with consuming RBC will drop significantly, also mortality after CABG will decline especially in women.

To conclude, women have another risk profile for cardiac surgery compared to men and therefore a worse outcome in mortality, preoperative risk factors predicts the outcome after CABG and not female gender. OPCAB is a better operation technique than CABG for women suffering CVD. Mortality after AVR is estimated by using the EuroSCORE, female gender may no longer need to be considered as a risk factor. Female gender is a significant independent risk factor for perioperative RBC transfusion.

Curriculum vitae

Franciscus Jozef (Joost) ter Woorst was born on March 10th 1960 in Arnhem, the Netherlands. After graduating from high school 'Canisius College Nijmegen' he started to study psychology at the State University of Utrecht. In 1979 he started his medical training at the State University of Utrecht. After graduating as medical doctor he joined the Military Service as medical doctor at the 11th Tank Bataljon in Oirschot.

In 1989 he worked as a resident at the department cardio-thoracic surgery in the Catharina Hospital Eindhoven and since 1990 at the department cardiothoracic surgery Academic Hospital Maastricht where he started his training under supervision of Prof. Dr. O.C.K.M. Penn. The last year of his training he went to the Academic Hospital of Utrecht under supervision of Prof. Dr. J.J. Bredeé. In July 1998 he joined the medical staff of the department cardiothoracic surgery of the Catharina Hospital Eindhoven until now. In 2007 untill 2014 he was Chairman of the cardiothoracic surgery department in Eindhoven. In 2009 he joined the board of the medical staff for 3 years as marketing/communication, constructive and ICT representative. In 2014 together with his colleagues of cardiothoracic surgery and cardiology he started the first combined cooperation 'Hartcentrum' in the Netherlands. From 2015 until now he is acting trainer for cardiothoracic surgery in Eindhoven and from 2018 until now he is a member of the Centrale Opleidings Commissie (COC).

From 2017 until this moment the papers of this thesis were published and the manuscript of this thesis was written.

Joost ter Woorst is married with Bettina and together they have 3 children: Carlijn, Sjoerd and Colette.

List of publications

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