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Sex-differences in outcome after off-pump coronary artery bypass grafting is age-dependent; data from the Netherlands Heart Registration

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A B S T R A C T

Background: Women are known to have worse outcome after coronary artery bypass grafting (CABG) than men. Studies have shown that off-pump coronary artery bypass grafting (OPCAB) might benefit higher-risk patients, and therefore might also benefit women. We aimed to determine differences in early and late outcomes between sexes after OPCAB.

Methods: Data from all patients undergoing OPCAB, between 2013 through 2021 was retrieved from the Netherlands Heart Registration (NHR) database. Primary outcomes were early mortality, morbidity and late survival. We divided the population into subgroups based on age (aged ≥70 years or < 70 years) and sex.

Results: This study included 8,487 men and 2,170 women (total = 10,657). Female patients received fewer anastomoses (mean (SD)) women 2.38 (1.17) vs men 2.68 (1.23), $p < 0.001$) and total arterial revascularization was performed less frequently in women than in men (21.3 % versus 29.5 % respectively, $p < 0.001$).

In the subgroup of patients <70 years, early mortality was 1.7 % in women and 0.6 % in men ($p < 0.001$). Survival rate at 5 years was 88.4 % in women and 91.1 % in men ($p < 0.001$). Female sex was associated with worse late survival in the subgroup <70 years (HR (95 % CI) 1.42 (1.10–1.83) $p = 0.008$).

Conclusions: Sex-differences in outcome after CABG persists in OPCAB surgery. However, these differences are solely present in the younger subgroup. In our data, women undergoing OPCAB surgery seem to be treated differently during surgery as compared to their male counter parts, further research is needed to analyze this finding.

1. Introduction

In cardiac surgery, coronary artery bypass grafting (CABG) is the most performed operation in adults [1]. It has been extensively described that women have a worse outcome after CABG in comparison to men. Mortality, both long-term and in-hospital or 30-day mortality, is higher among women [2,3]. This difference is especially evident among younger women [4].

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[1] See addendum for Cardiothoracic Surgery Registration Committee members of the Netherlands Heart Registration.

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Abbreviations and acronyms

BMI	body mass index
BSA	Body surface area
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CI	Confidence interval
ECC	extra-corporeal circulation
HR	Hazard ratio
ICU	Intensive care unit
IQR	Inter quartile range
LIMA	left internal mammary artery
LVEF	left ventricular ejection fraction
MEC-U	The Medical Research Ethics Committee
NHR	Netherlands Heart Registration
ONCAB	On-pump coronary artery bypass grafting
OPCAB	Off-pump coronary artery bypass grafting
PCI	Percutaneous coronary intervention
LVEF	left ventricular ejection fraction
SD	Standard deviation
SVG	saphenous vein grafts

Studies have shown, however, that the off-pump coronary artery bypass grafting (OPCAB) technique might benefit women, and might even close the gap in outcome for men and women [5]. Several studies showed better early and late survival for women after OPCAB surgery [5,6]. The exact role which OPCAB plays concerning the improved outcome in women undergoing surgery is still unclear. The avoidance of the extra-corporeal circulation (ECC) might play a role as the use of ECC increases systemic inflammation and platelet activation [7]. This, however, does not explain why women benefit more from OPCAB than men. Other studies have shown that women undergoing OPCAB tend to receive more internal thoracic artery grafts compared to women undergoing on-pump coronary artery bypass grafting (ONCAB) and thus resulting in a difference in surgical approach between women undergoing OPCAB and ONCAB surgery [8].

The aim of this study was to determine whether women benefit more from OPCAB than men do, and to investigate if sex-differences in outcomes persist in OPCAB surgery. We compared data on both early and late outcomes in patients who underwent OPCAB in the Netherlands between 2013 and 2021.

2. Patients and methods

2.1. Study population

The data included in this study are retrieved from the national database of the Netherlands Heart Registration (Nederlandse Hart Registratie, NHR). This prospective compulsory database comprises data of all the patients who underwent cardiac surgery in the Netherlands. The process and rationale behind data collection was reported elsewhere [9]. The database contains a variety of data on cardiac surgical procedures performed in the Netherlands. In addition to demographic characteristics and type of intervention, the database also includes parameters concerning postoperative morbidity and mortality and all the risk factors that are required for the calculation of the most frequently used risk scores, such as the EuroSCORE [10]. Participation in this registry by departments of cardiothoracic surgery in the Netherlands was defined as compulsory by the Dutch Society of Cardiothoracic Surgery as part of their quality policy. Although this database was initiated for quality evaluation of cardiovascular interventions, its adequacy in registering compulsory pre- and post-operative variables enables long-term follow-up of patients undergoing cardiac surgical interventions.

2.2. Ethical statement

The Medical Research Ethics Committee (MEC-U) waived the need for informed consent (W19.270).

2.3. Inclusion

Patients were included in the analysis if they were 18 years and older and had undergone isolated OPCAB.

2.4. Study design

The study was designed as a retrospective multi-center cohort study of prospectively collected data from 16 cardiothoracic centers in the Netherlands. Data was collected for patients who underwent OPCAB between 2013 and 2021.

2.5. Outcomes

The NHR database was searched for all pre-operative data and baseline characteristics required for the calculation of the EuroSCORE I. Short-term outcomes that were retrieved from the database included early mortality (30-day mortality), postoperative complications (stroke, myocardial infarction, pneumonia, re-intubation, prolonged ventilation, re-admission to the intensive care, renal failure, gastro-intestinal complications, re-exploration for bleeding and arrhythmia) and duration of hospital stay. Definitions of postoperative complications are provided in appendix 2.

Survival follow-up was last checked on March 1st' 2022. During late follow-up, all-cause mortality was derived from the municipal administration records and was completed for all patients.

2.6. Missing values

The national database of the NHR has an exceptionally high data completeness for baseline characteristics. Only 201 patients (1.9 %) were lost-to-follow-up and therefore not included in late mortality analysis.

2.7. Statistical analysis

Normality of the continuous variables was tested by visual inspection of the histograms and the Shapiro–Wilk test. Continuous variables are presented as mean ± SD, in case of skewedness, and as median with interquartile range (IQR). Categorical data are expressed as frequencies and percentages and were compared using the χ^2 test. If the minimum expected cell-size assumption did not apply, data were analyzed with Fisher's exact test. Continuous variables were compared using *t*-test or in case of non-normally distributed data with the Mann-Whitney *U* test. Late survival was demonstrated with Kaplan-Meier survival curves. Subgroup analysis was performed for male and female patients younger than 70 years, based on the recommendation of the current guidelines for conduit selection [9]. Differences between survival curves were assessed using the Log-Rank test. The variables that were associated with late mortality were identified using Cox regression. Here independent variables with a significance level $p < 0.05$ in the univariate model were entered in the multivariate model. Hazard ratios (HR) are reported with associated 95 % confidence intervals (CI). All reported p-values were 2-sided and were considered statistically significant if $P < 0.05$. Statistical analyses of the data were performed using SPSS software (V26, IBM, Armonk, New York, USA) and R Statistics (the R Foundation, Vienna, Austria).

Table 1
Baseline characteristics total population.

Baseline characteristics	Males	Females	p-*value*
n (%)	n = 8,487	n = 2,170	
Age, median [IQR]	66 [59–73]	70 [63–76]	**<0.001**
BMI, median [IQR]	27.5 [24.9–29.5]	27.5 [24.3–30.1]	0.23
BSA, median [IQR]	2.01 [1.93–2.14]	1.81 [1.70–1.95]	**<0.001**
Diabetes	2,009 (23.7)	643 (29.6)	**<0.001**
COPD	844 (9.9)	236 (10.9)	0.20
PVD	1,202 (14.2)	356 (16.4)	**0.01**
Serum creatinine (>200μm/L)	164 (1.9)	35 (1.5)	0.33
Recent myocardial infarction	2,700 (31.8)	692 (31.9)	0.95
Unstable AP	703 (8.3)	205 (9.4)	**0.08**
Prior cardiac surgery	231 (2.7)	73 (3.4)	0.11
Prior CABG	189 (2.2)	56 (2.6)	0.33
LV function			**<0.001**
LVEF >50 %	5,734 (67.6)	1,576 (72.6)	
LVEF 31–50 %	2,266 (26.7)	488 (22.5)	
LVEF 21–30 %	317 (3.7)	69 (3.2)	
LVEF 20 % or less	54 (0.6)	11 (0.5)	
Unknown	116 (1.4)	26 (1.2)	
Urgency			**0.01**
Elective	4,514 (53.2)	1,080 (49.8)	
Urgent	3,571 (42.1)	957 (44.1)	
Emergency	279 (3.3)	93 (4.3)	
Salvage	55 (0.6)	21 (1.0)	
Unknown	68 (0.8)	19 (0.9)	
EuroSCORE I, median [IQR]	2.50 [1.51–4.62]	4.41 [2.45–7.80]	**<0.001**

Abbreviations: AP,:angina pectoris; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; IQR,interquartile range; LV, left ventricle; LVEF, left ventricular ejection fraction; PVD, peripheral vascular disease.

3. Results

3.1. Baseline characteristics

A total of 10,657 patients underwent OPCAB surgery between 2013 and 2021 in the Netherlands. The majority of the patients who received OPCAB surgery were male (n = 8,487, 80 %). Women were older at time of surgery (age in years, median [IQR]: Men 66 [59–73] vs women 70 [63–76], p < 0.001), and suffered more frequently from diabetes and peripheral vascular disease (PVD). No differences in BMI was observed between men and women (27.5 [24.9–29.5] vs 27.5 [24.3–30.1]; P = 0.23). Multivessel disease was seen in 74.7 % of men and 69.1 % of women P = 0.01. Further data are shown in Table 1. Among the total cohort, women more frequently presented for emergency surgery. These differences led to a higher median EuroSCORE I for women undergoing OPCAB than for men (4.41 [2.45–7.80] vs 2.50 [1.51–4.62] respectively, p < 0.001) (Table 1). When comparing men and women <70 years women suffered more from diabetes (29.2 % vs 21.0 % p < 0.001*)*, had more PVD (15.5 % vs 10.1 %, p < 0.001*)*, had more frequently prior cardiac surgery and underwent more emergency operation. However, women had a better preoperative left ventricular function than men. In the older patient population, we found that men suffered more from PVD (20.7 % vs 17.2 %, p = 0.01) and had a worse kidney function. In both groups (<70 and ≥ 70 years) women had a higher EuroSCORE I. Further details on baseline characteristics of the total cohort and the subgroups based on age are shown in Table 1 and Table 2.

3.2. Operative characteristics

Women received fewer anastomoses compared to men (mean (SD) 2.38 (1.17) vs 2.68 (1.23), respectively) This applied for all age groups. Younger women received fewer distal anastomosis compared to women ≥70 years. Arterial (≥2 arterial grafts) bypass grafting was performed less frequently in women compared to men (21.3 % vs 29.5 % p = 0.001).

Arterial revascularization with ≥2 arterial grafts occurred in 35.5 % of male patients <70 years, whereas 25.8 % of female patients <70 years received ≥2 arterial grafts *(*p = 0.001). In men ≥70 years, 19.8 % of patients received ≥2 arterial grafts, and 17.3 % of women ≥70 years received ≥2 arterial grafts (p = 0.17).

3.3. Early outcomes

There was no statistically significant difference in 30-day mortality between women and men ≥70 years (3.4 % vs 2.3 %, respectively (p = 0.06*))*. However, there was a statistically significant difference between women and men aged <70 years (men 0.6 % versus women 1.7 %, p < 0.001).

Table 2
Baseline characteristics in the age subgroups.

	<70			≥70		
n (%)	**Male**	**Female**	**p-*value***	**Male**	**Female**	**p-*value***
	n = 5,256	n = 1,036		n = 3,231	n = 1,134	
Age, median [IQR]	61 [55–65]	63 [56–66]	**<0.001**	74 [72–78]	75 [72–79]	**<0.001**
BMI, median [IQR]	27.6 [25.2–30.1]	27.6 [24.5–30.6]	0.14	26.9 [24.6–28.7]	27.3 [24.2–29.7]	0.18
BSA, median [IQR]	2.04 [1.96–2.17]	1.83 [1.72–1.97]	**<0.001**	2.00 [1.90–2.08]	1.79 [1.68–1.92]	**<0.001**
Diabetes	1,102 (21)	302 (29.2)	**<0.001**	907 (28.1)	341 (30.1)	0.20
COPD	437 (8.3)	105 (10.1)	0.06	407 (12.6)	131 (11.6)	0.36
PVD	532 (10.1)	161 (15.5)	**<0.001**	670 (20.7)	195 (17.2)	**0.01**
Serum creatinine (>200µm/L)	76 (1.4)	21 (2.0)	0.17	88 (2.7)	14 (1.2)	**0.01**
Recent myocardial infarction	1,723 (32.8)	315 (30.4)	0.14	977 (30.2)	377 (33.2)	0.06
Unstable AP	433 (8.2)	90 (8.7)	0.63	270 (8.4)	115 (10.1)	0.07
Prior cardiac surgery	121 (2.3)	36 (3.5)	**0.03**	110 (3.4)	37 (3.3)	0.82
Prior bypass surgery	99 (1.9)	26 (2.5)	0.19	90 (2.8)	30 (2.6)	0.80
LV function			**0.03**			**0.001**
LVEF >50 %	3,644 (69.3)	771 (74.4)		2,090 (64.7)	805 (71.0)	
LVEF 31–50 %	1,314 (25)	219 (21.1)		952 (29.5)	269 (23.7)	
LVEF 21–30 %	183 (3.5)	29 (2.8)		134 (4.1)	40 (3.5)	
LVEF 20 % or less	38 (0.7)	6 (0.6)		16 (0.5)	5 (0.4)	
Unknown	77 (1.5)	11 (1.1)		39 (1.2)	15 (1.3)	
Urgency			**0.10**			0.13
Elective	2,860 (54.4)	533 (51.4)		1,654 (51.2)	547 (48.2)	
Urgent	2,134 (40.6)	438 (42.3)		1,437 (44.5)	519 (45.8)	
Emergency	175 (3.3)	42 (4.1)		104 (3.2)	51 (4.5)	
Salvage	37 (0.7)	14 (1.4)		18 (0.6)	7 (0.6)	
Unknown	50 (1.0)	9 (0.9)		18 (0.6)	10 (0.9)	
EuroSCORE I, median [IQR]	1.61 [1.17–2.73]	2.35 [1.73–4.26]	**<0.001**	4.51 [3.01–7.65]	6.58 [4.31–10.06]	**<0.001**

Abbreviations: AP, angina pectoris; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LV, left ventricle; LVEF, left ventricular ejection fraction; PVD, peripheral vascular disease.

The length of hospital stay was significantly longer for women than for men, regardless of their age. Women more frequently suffered from stroke in the postoperative period compared to men (0.6 % versus 1.1 %, p = 0.01).

Female patients <70 years more frequently suffered from deep sternal wound infections than men. (1.2 % vs 0.6 % respectively p = 0.03). Further data on hospital stay and postoperative complications can be found in Tables 3 and 4.

3.4. Late outcomes

At 5-year follow-up, the survival rate was 90.5 %. Survival rate at 5-years was 91.1 % in male patients, compared to 88.4 % in female patients (p < 0.001). In patients 70 years and older, no significant difference in late survival was observed between men and women (p = 0.60). In the subgroup analysis for patients younger than 70 years, a significantly worse late survival was found in women (92.2 %) compared to men (95.3 %) (p < 0.001). (Fig. 1).

In the total cohort, multivariate Cox regression analysis (Tables 5 and 6) revealed the following independent risk factors for late mortality: age, female sex, diabetes, chronic obstructive pulmonary disease (COPD), PVD, serum creatinine >200 μm/L, unstable angina pectoris, prior cardiac surgery, and reduced LVEF <50 %.

In the subgroup <70 years, we found that female sex, age, diabetes, COPD, PVD, serum creatinine >200 μm/L and LVEF <50 % were associated with worse late survival.

Among the subgroup ≥70 years, we did not find female sex to be an independent risk factor for worse late survival. Age, BMI, diabetes, COPD, PVD, serum creatinine >200 μm/L, unstable angina pectoris, non-elective surgery and LVEF <50 % were variables that were independently associated with worse late survival.

4. Comment

The main findings of the present study are that sex-difference in outcome after CABG persists among a population treated with OPCAB surgery. The differences in outcomes are especially evident among the study population <70 years. We found a significantly worse 30-day mortality and 5-years survival for women in this subgroup. Additionally, we found that female sex is an independent predictor of worse late survival after OPCAB surgery in the subgroup <70 years.

Considerable evidence has been established that women undergoing ONCAB have a higher operative mortality as compared to men [11,12]. A large study from the STS national cardiac surgery database, on which the STS score is established, demonstrated operative mortality after CABG to be 3.54 % for women and 2.15 % for men [11].

Our study population, that were solely treated with OPCAB surgery, demonstrated similar differences in 30-day mortality between women and men (2.6 % vs 1.2 % respectively).

Younger women seem to have a worse outcome compared to their male counterparts, and this difference in outcome seems to reduce as women age. Among elderly, female sex does not seem to be a risk factor for worse outcomes after CABG. This pattern has been described by several studies on CABG but so far not solely on OPCAB patients [13]. A difference in outcomes after OPCAB surgery between older and younger women could possibly be attributed to a difference in disease patterns and risk profile.

Puskas et al. described a reduction in risk difference between men and women undergoing off-pump surgery, as compared to on-pump CABG [14]. This effect has been described by several other authors [15,16]. However, in these studies, the population was not divided into age groups. Contrary to the claims of these articles, we found that disparity in outcomes between sexes in the younger

Table 3
Operative and postoperative data total population.

Variables	Total Male Population	Total Female Population	p-value
n (%)	n = 8,487	n = 2,170	
Arterial (2≥ arterial grafts)	2,505 (29.5)	463 (21.3)	**0.001**
Number of anastomosis, median [IQR]	3 [2–4]	2 [1–3]	**<0.001**
Number of anastomosis, mean (SD)	2.68 (1.23)	2.38 (1.17)	**<0.001**
Arm/leg wound infection	24 (0.3)	8 (0.4)	0.51
Deep sternal wound infection	64 (0.8)	25 (1.2)	0.07
Urinary tract infection	50 (0.6)	22 (1)	**0.03**
Pneumonia	282 (3.3)	47 (2.2)	**0.01**
Reintubation due to respiratory insufficiency	109 (1.3)	29 (1.3)	0.85
Prolonged intubation (>24 h)	222 (2.6)	68 (3.1)	0.19
Re-admission to ICU	202 (2.4)	55 (2.5)	0.68
Stroke	49 (0.6)	23 (1.1)	**0.01**
Vascular complications	7 (0.1)	3 (0.1)	0.45
Gastrointestinal complications	48 (0.6)	6 (0.3)	0.09
Renal failure	65 (0.8)	19 (0.9)	0.61
New-onset arrhythmia	1,862 (21.9)	503 (23.2)	0.22
Re-exploration	311 (3.7)	71 (3.3)	0.38
Length of hospital stay in days, median [IQR]	5 [4–7]	5 [4–7]	**<0.001**
30-day mortality	104 (1.2)	56 (2.6)	**0.001**

Abbreviations: IQR, interquartile range; ICU, intensive care unit; SD, standard deviation.

Table 4
Operative and postoperative data in the age subgroups.

Variables	<70			≥70		
	Male	Female	p-*value*	Male	Female	p-*value*
	n = 5,256	n = 1,036		n = 3,231	n = 1,134	
Arterial (2≥ arterial grafts)	1,864 (35.5)	267 (25.8)	**0.001**	641 (19.8)	196 (17.3)	0.17
Number of anastomosis, median [IQR]	3 [2–3]	2 [1–3]	**0.001**	3 [2–4]	2 [1–3]	**<0.001**
Number of anastomosis, mean (SD)	2.62 (1.22)	2.32 (1.19)	**0.001**	2.76 (1.24)	2.44 (1.15)	**<0.001**
Arm/leg wound infection	13 (0.2)	4 (0.04)	0.51	11 (0.3)	4 (0.04)	0.99
Deep sternal wound infection	30 (0.6)	12 (1.2)	**0.03**	34 (1.1)	13 (1.1)	0.79
Urinary tract infection	22 (0.4)	10 (1.0)	**0.02**	28 (0.9)	12 (1.1)	0.56
Pneumonia	140 (2.7)	26 (2.5)	0.78	142 (4.4)	21 (1.9)	**<0.001**
Reintubation due to respiratory insufficiency	61 (1.2)	14 (1.4)	0.61	48 (1.5)	15 (1.4)	0.69
Prolonged intubation (>24 h)	122 (2.3)	33 (3.2)	0.10	100 (3.1)	35 (3.1)	0.99
Re-admission to ICU	92 (1.8)	24 (2.3)	0.22	110 93.4)	31 (2.7)	0.27
Stroke	24 (0.5)	8 (0.8)	0.19	25 (0.8)	15 (1.3)	0.10
Vascular complications	4 (0.10)	2 (0.2)	0.26	3 (0.1)	1(0.1)	0.99
Gastrointestinal complications	29 (0.6)	4 (0.4)	0.50	19 (0.6)	2 (0.2)	0.09
Kidney failure	32 (0.6)	7 (0.7)	0.80	33 (1.0)	12 (1.1)	0.92
New-onset arrhythmia	929 (17.7)	187 (18.1)	0.77	933 (28.9)	316 (27.9)	0.52
Re-exploration for bleeding	196 (3.7)	25 (2.4)	**0.04**	115 (3.6)	46 (4.1)	0.45
Length of hospital stay in days, median [IQR]	5 [4–6]	5 [4–7]	**0.001**	5 [4–7]	6 [4–7]	**0.01**
30-day mortality	30 (0.6)	18 (1.7)	**<0.001**	74 (2.3)	38 (3.4)	0.06

Abbreviations: IQR, interquartile range; ICU, intensive care unit; SD, standard deviation.

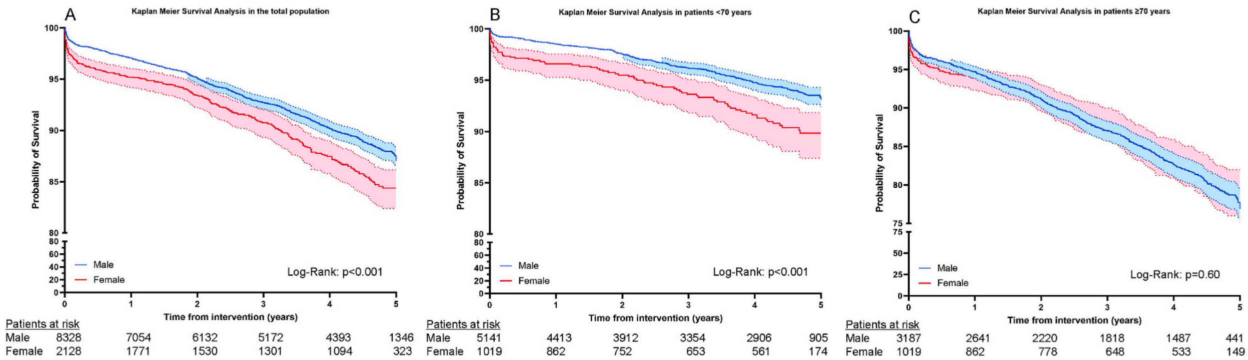

Fig. 1. A Kaplan-Meier total population (men vs women), **B** <70 years (men vs women) and **C** <=70 years (men vs women)

Table 5
Univariate Cox-regression analyses for late mortality.

	All patients		70 year		≥70 year	
Variable	**Univariate analysis**	**p-value**	**Univariate analysis**	**p-value**	**Univariate analysis**	**p-value**
	HR (95 % CI)		**HR (95 % CI)**		**HR (95 %)**	
Female sex	1.32 (1.15–1.53)	**<0.001**	1.67 (1.30–2.15)	**<0.001**	0.96 (0.80–1.14)	0.6
Age	1.08 (1.07–1.09)	**0.001**	1.08 (1.06–1.10)	**<0.001**	1.08 (1.06–1.10)	**<0.001**
BMI	0.97 (0.96–0.99)	**<0.001**	1.00 (0.97–1.02)	0.71	0.98 (0.96–1.00)	**0.03**
Diabetes	1.84 (1.62–2.09)	**<0.001**	2.02 (1.61–2.53)	**0.001**	1.54 (1.32–1.80)	**0.001**
COPD	2.38 (2.04–2.77)	**<0.001**	2.66 (2.03–3.50)	**0.001**	1.96 (1.63–2.36)	**<0.001**
PVD	2.13 (2.75–3.57)	**<0.001**	4.46 (3.55–5.60)	**<0.001**	2.14 (1.82–2.52)	**<0.001**
Serum creatinine (>200μm/L)	5.87 (4.67–7.37)	**<0.001**	8.77 (6.12–12.57)	**<0.001**	4.21 (3.13–5.66)	**<0.001**
Recent myocardial infarction	1.22 (1.07–1.38)	**0.01**	1.19 (0.95–1.49)	0.13	1.32 (1.12–1.54)	**<0.001**
Unstable AP	1.60 (1.33–1.92)	**<0.001**	1.60 (1.16–2.20)	**0.01**	1.59 (1.27–1.98)	**0.001**
Prior cardiac surgery	1.77 (1.32–2.38)	**<0.001**	1.63 (0.93–2.83)	0.09	1.68 (1.19–2.38)	**0.01**
Non-elective surgery	1.44 (1.27–1.63)	**<0.001**	1.41 (1.13–1.75)	**0.01**	1.43 (1.22–1.66)	**<0.001**
LVEF <50 %	2.00 (1.77–2.26)	**<0.001**	2.76 (2.23–3.43)	**0.001**	1.58 (1.36–1.84)	**0.001**
2≥ Arterial grafts	0.71 (0.61–0.82)	**<0.001**	0.65 (0.51–0.83)	**<0.001**	1.01 (0.88–1.17)	0.88

Abbreviations: AP, angina pectoris; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; PVD, peripheral vascular disease.

Table 6
Multivariate Cox regression analysis for late mortality.

	All patients		<70 years		≥70 years	
Variables	**Multivariate analysis**	**p-value**	**Multivariate analysis**	**p-value**	**Multivariate analysis**	**p-value**
	HR (95 % CI)		**HR (95 %)**		**HR (95 %)**	
Female sex	1.17 (1.01–1.36)	**0.03**	1.42 (1.10–1.83)	**0.01**	1.02 (0.86–1.22)	0.80
Age	1.07 (1.06–1.08)	**<0.001**	1.06 (1.04–1.08)	**<0.001**	1.07 (1.05–1.09)	**<0.001**
BMI	0.98 (0.96–1.00)	**0.01**			1.07 (1.05–1.09)	**0.02**
Diabetes	1.49 (1.30–1.70)	**<0.001**	1.46 (1.15–1.84)	**0.002**	1.47 (1.25–1.73)	**<0.001**
COPD	1.75 (1.50–2.05)	**<0.001**	1.93 (1.46–2.55)	**<0.001**	1.68 (1.39–2.03)	**<0.001**
PVD	2.03 (1.77–2.33)	**<0.001**	2.67 (2.10–3.40)	**<0.001**	1.76 (1.49–2.09)	**<0.001**
Serum creatinine (>200μm/L)	3.70 (2.92–4.70)	**<0.001**	4,85 (3.33–7.06)	**<0.001**	3.03 (2.23–4.13)	**<0.001**
Recent myocardial infarction	1.06 (0.92–1.22)	0.40	1.05 (0.82–1.34)	0.72	1.08 (0.91–1.28)	0.36
Unstable AP	1.28 (1.06–1.56)	**0.01**	1.24 (0.88–1.74)	0.22	1.29 (1.02–1.62)	**0.04**
Prior cardiac surgery	1.37 (1.02–1.84)	**0.04**	1.16 (0.66–2.02)	0.61	1.46 (1.03–2.07)	0.32
Non elective Surgery	1.21 (1.05–1.38)	**0.01**	1.18 (0.92–1.50)	0.19	1.22(1.04–1.44)	**0.02**
LVEF <50 %	1.62 (1.43–1.84)	**<0.001**	2.12 (1.69–2.67)	**<0.001**	1.38 (1.18–1.61)	**<0.001**
2≥ Arterial grafts	1.01 (0.89–1.15)	0.85	0.86 (0.67–1.09)	0.21		

Abbreviations: AP, angina pectoris; BMI, body mass index; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; PVD, peripheral vascular disease.

subgroup after CABG remains among patients treated with off-pump surgery. In concordance with these studies, we found that the mortality rate in older patients was similar between men and women undergoing off-pump CABG. Several studies have described a benefit of off-pump CABG for high-risk patients [17,18].

A reduced inflammatory response, difference in platelet activation and reduced hemodilution when surgery is performed without ECC are suggested explanations for the reduced 30-day mortality in patients undergoing OPCAB surgery. Bypass surgery in both off-pump and on-pump surgery causes an extensive inflammatory response [19]. Struber et al. found a reduced inflammatory response in patients undergoing OPCAB surgery as compared to patients undergoing ONCAB surgery [20]. However, most OPCAB surgeries were performed through a small lateral thoracotomy, reducing the size of the operation site, which likely contributed to this reduced inflammatory response. According to Czerny et al., off-pump surgery causes considerably less myocardial injury than ONCABG and could thereby benefit high-risk patients was well [21].

Red blood cell transfusion has been associated with decreased long-term survival in cardiac surgery [22]. Studies have described a reduced demand for peri-operative blood transfusion in off-pump surgery due to the smaller dose of heparin used, and a decreased dilution of coagulation factors without ECC use [23–25]. Reduced use of blood-products might be one of the benefits of off-pump surgery.

Our study contributes to the mounting evidence that women present for OPCAB surgery with a different risk profile than men do. Estrogen, and its protective effects on the cardiovascular system might play a role in this phenomenon. Women have a lower risk of coronary artery disease (CAD) before menopause due to estrogen while the risk of CAD increases after menopause,. Over time, the risk becomes equal to the risk of developing CAD in men. It has been extensively described that woman who had difficulties in their reproductive health, and thus had lower levels of estrogen, have a higher risk of cardiovascular disease and CAD. Whether the lack of estrogen also contributes to the different disease pattern in women and younger women presenting with CAD is still understudied [26].

Differences in surgical techniques such as used in OPCAB might provide benefits for high-risk patients and might benefit women more than men due to the sex-differences in preoperative risk factors. Side-clamp usage in OPCAB surgery decreases the benefit which OPCAB offers with regards to stroke incidence reduction in patients with a heavily calcified ascending aorta [27]. No-touch aorta technique, which is solely possible in off-pump surgery, has been demonstrated to decrease stroke rates with as much as 60 % as compared to traditional side-clamp OPCAB, was described in the meta-analysis by Pawliszak et al. [28] Stroke rates appear to be higher among women who require coronary revascularization [29]. Reducing this risk by using the no-touch aorta technique might explain why studies have found a reduced morbidity and mortality in women undergoing OPCAB surgery.

Another interesting finding in our study was the positive effect of the use of two or more arterial grafts in younger patients. The positive effect of using arterial graft material has been extensively described in several observational studies and in reviews [30]. Bilateral mammary artery use, as well as the use of the radial artery in T- or Y- graft construction with the left internal mammary artery (LIMA) have been mentioned as safe alternatives to LIMA and saphenous vein grafts (SVG). In addition to being a safe alternative, these techniques might also lead to a decreased long-term and short-term mortality, and facilitate the no-touch aorta technique [30].

Women present with a higher risk profile when they are referred for surgery [31]. The possible benefits that OPCAB brings in high-risk patients as described above might be an explanation why several studies have found a risk reduction for women undergoing OPCAB surgery. We did, however, find a difference in outcome between male and female patients undergoing OPCAB. Whether this difference in outcomes between sexes is similar to the difference seen in CABG patients requires further investigation.

5. Limitations

The current study has some limitations, mostly due to the retrospective nature of the study. The primary endpoint of the study is all-cause mortality. The registry does not include the cause of death, which could be relevant for the interpretation of mortality rates.

6. Conclusions

With our study, we demonstrate that the differences in outcome between men and women, known to be present in ONCAB patients are still present in patients undergoing OPCAB surgery. These differences are solely demonstrated in the younger subgroup (<70 years), and were not demonstrated in the older subgroup (≥70 years). Female sex was retrieved as an independent variable associated with late survival in the subgroup <70 years. However, female sex was not an independent variable in the population ≥70 years. Our data also shows that women undergoing OPCAB are treated differently during surgery compared to men.

Clinical perspectives

In this study, we demonstrated that OPCAB surgery in the Netherlands carries similar risks and benefits for women as has been earlier reported regarding on-pump CABG. This study encourages further research, not only into the pathophysiology of CAD in (younger) women, but also into a suitable operative approach for CAD in (younger) women.

CRediT authorship contribution statement

Mara-Louise Wester: Writing – original draft, Methodology, Investigation, Data curation. **Jules R. Olsthoorn:** Writing – review & editing, Validation, Formal analysis, Data curation. **Saskia Houterman:** Writing – review & editing, Validation, Supervision, Formal analysis, Data curation, Mohamed A, Writing – review & editing, Supervision, Methodology. **Maaike M. Roefs:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Angela HEM. Maas:** Writing – review & editing, Validation, Supervision. **Joost FJ. ter Woorst:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23899.

Appendix 2

Definitions according to the Netherlands Heart Registration.

Pneumonia

Lung infection/pneumonia with positive sputum cultures.

Urinary tract infection

Infection with positive urine culture.
Reintubation due to respiratory insufficiency.
Respiratory failure requiring reintubation.

Prolonged intubation (>24 h)

Ventilation for more than 24 h.

Readmission to ICU

Readmission to the Intensive Care Unit (ICU) or Post Anesthesia Care Unit (PACU) after initial discharge from the IC/PACU. This does not include a stay in the Medium Care (MC).

Stroke

The combined endpoint of stroke without neurological deficit and stroke with neurological deficit.

Stroke without neurological deficit

A neurologist has determined that a central neurological deficit (CVA) during the postoperative period has occurred, but with no residual injury at discharge.

This also includes a Transient Ischemic Attack (TIA).

Stroke with neurological deficit

A neurologist has determined that a postoperative stroke has occurred during the hospitalization for the current intervention (excluding TIA).

CVA = permanent neurological dysfunction diagnosed by a neurologist as due to focal ischemia of the brain, spinal cord, or retina, caused by an acute infarction of the neurological tissue due to thrombosis, embolism, systemic hypoperfusion or bleeding.

Kidney failure

Renal failure that occurs if one or more of the following STS criteria are met during the postoperative period.

- Renal replacement therapy (dialysis, CVVH) which was not initiated preoperatively
- Highest postoperative creatinine value > 177 μmol/L and doubling of the preoperative value (preoperative value being the value of the creatinine used to calculated the EuroSCORE).

Gastro-intestinal complications

Bleeding: gastrointestinal bleeding requiring therapy such as transfusion, scope or surgery.

Other: intestinal ischemia, acalculous cholecystitis.

Vascular complications

The occurrence of any vascular complications during hospitalization, diagnosis according to the VARC-2 definitions, from the start of the current intervention.

(including peroperative vascular complications and excluding stroke).

New-onset arrhythmia

All forms of de novo rhythm problems requiring treatment (such as resuscitation in connection with asystole, new onset atrial fibrillation/flutter for which specific intervention (defibrillation, medication) is necessary). This does not include: a spontaneously transient period of atrial fibrillation, without any consequence for the patient.

Mediastinitis

Deep sternal wound infection (mediastinitis) within 30 days. Includes muscle, sternum, mediastinum and is positive if one or more of the following criteria is present:

- Surgical drainage/sternum refixation in deep sternum wound infection
- Positive wound cultures.
- AB therapy due to the sternum wound.

This includes a deep sternal wound infection that occurred after the patient was discharged from the hospital.

Reexploration (within 30 days)

Rethoracotomy within 30 days after initial surgery due to a complication of the current intervention. This also includes rethoracotomies performed after the patient has been discharged.

This concerns the first rethoracotomy after the initial closing of the thorax. This applies to all causes, with the exception of opening the sternum in due to mediastinitis or refixation of the sternum.

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