Females have an increased risk of short-term mortality after cardiac surgery compared to males: Insights from a national database

Lauren Dixon[1], Arnaldo Dimagli[1], Ettorino Di Tommaso[1], Shubhra Sinha[1], Daniel Fudulu[1], Manraj Sandhu[1], Umberto Benedetto[1], and Gianni Angelini[1]

[1]Bristol Heart Institute University of Bristol Bristol UK

February 22, 2024

Abstract

Objectives: Female sex is considered a risk factor for mortality and morbidity following cardiac surgery. This study is the first to review the UK adult cardiac surgery national database to compare outcomes following surgical coronary revascularisation and valvular procedures between females and males. Methods: Using data from National Adult Cardiac Surgery Audit (NACSA), we identified all elective and urgent, isolated coronary artery by-pass grafting (CABG), aortic valve replacement (AVR) and mitral valve replacement/repair (MVR) procedures from 2010-2018. We compared baseline data, operative data and outcomes of mortality, stroke, renal failure, deep sternal wound infection, return to theatre for bleeding and length of hospital stay. Multivariable mixed-effect logistical/linear regression models were used to assess relationships between sex and outcomes, adjusting for baseline characteristics. Results: Females, compared to males, had greater odds of experiencing 30-day mortality (CABG OR 1.76, CI 1.47-2.09, $p<0.001$; AVR OR 1.59, CI 1.27-1.99, $p<0.001$; MVR OR 1.37, CI 1.09-1.71, $p=0.006$). After CABG, females also had higher rates of post-operative dialysis (OR 1.31, CI 1.12-1.52, $p<0.001$), deep sternal wound infections (OR 1.43, CI 1.11-1.83, $p=0.005$) and longer length of hospital stay (Beta 1.2, CI 1.0-1.4, $p<0.001$) compared to males. Female sex was protective against returning to theatre for post-operative bleeding following CABG (OR 0.76, CI 0.65-0.87, $p<0.001$) and AVR (OR 0.72, CI 0.61-0.84, $p<0.001$). Conclusion: Females in the UK have an increased risk of short-term mortality after cardiac surgery compared to males. This highlights the need to focus on the understanding of the causes behind these disparities and implementation of strategies to improve outcomes in females.

Females have an increased risk of short-term mortality after cardiac surgery compared to males: Insights from a national database

Lauren Kari Dixon, Arnaldo Dimagli, Ettorino Di Tommaso, Shubhra Sinha, Daniel Paul Fudulu, Manraj Sandhu, Umberto Benedetto, Gianni D. Angelini

Bristol Heart Institute, University of Bristol, Bristol, UK

Corresponding Author :

Professor G.D. Angelini

Bristol Heart Institute,

Bristol,

BS2 8HW

Email: G.D.Angelini@bristol.ac.uk

Other Authors:

Lauren Kari Dixon: lauren.dixon@bristol.ac.uk

Arnaldo Dimagli: arnaldo.dimagli@bristol.ac.uk

Ettorino Di Tommaso: fq18031@bristol.ac.uk

Shubhra Sinha: shubhra.sinha@doctors.org.uk

Daniel Paul Fudulu: daniel.fudulu@bristol.ac.uk

Manraj Sandhu: manraj.s.sandhu@gmail.com

Umberto Benedetto: umberto.benedetto@bristol.ac.uk

Word Count:

Abstract

Objectives : Female sex is considered a risk factor for mortality and morbidity following cardiac surgery. This study is the first to review the UK adult cardiac surgery national database to compare outcomes following surgical coronary revascularisation and valvular procedures between females and males.

Methods: Using data from National Adult Cardiac Surgery Audit (NACSA), we identified all elective and urgent, isolated coronary artery by-pass grafting (CABG), aortic valve replacement (AVR) and mitral valve replacement/repair (MVR) procedures from 2010-2018. We compared baseline data, operative data and outcomes of mortality, stroke, renal failure, deep sternal wound infection, return to theatre for bleeding and length of hospital stay. Multivariable mixed-effect logistical/linear regression models were used to assess relationships between sex and outcomes, adjusting for baseline characteristics.

Results: Females, compared to males, had greater odds of experiencing 30-day mortality (CABG OR 1.76, CI 1.47-2.09, $p<0.001$; AVR OR 1.59, CI 1.27-1.99, $p<0.001$; MVR OR 1.37, CI 1.09-1.71, $p=0.006$). After CABG, females also had higher rates of post-operative dialysis (OR 1.31, CI 1.12-1.52, $p<0.001$), deep sternal wound infections (OR 1.43, CI 1.11-1.83, $p=0.005$) and longer length of hospital stay (Beta 1.2, CI 1.0-1.4, $p<0.001$) compared to males. Female sex was protective against returning to theatre for post-operative bleeding following CABG (OR 0.76, CI 0.65-0.87, $p<0.001$) and AVR (OR 0.72, CI 0.61-0.84, $p<0.001$).

Conclusion: Females in the UK have an increased risk of short-term mortality after cardiac surgery compared to males. This highlights the need to focus on the understanding of the causes behind these disparities and implementation of strategies to improve outcomes in females.

Key Words: Sex. Gender. Cardiac Surgery. CABG. AVR. MVR. Mortality. Disparities

Glossary of Abbreviations:

CABG: Coronary artery bypass graft

AVR: Aortic valve replacement

MVR: Mitral valve repair or replacement

LIMA: Left internal mammary artery

RIMA: Right internal mammary artery

BIMA: Bilateral internal mammary arteries

MI: Myocardial infarction

CPB: Cardio-pulmonary bypass

SD: Standard deviation

IQR: Interquartile range

OR: Odds Ratio

HR: Hazard Ratio

CI: Confidence interval

NACSA: National Adult Cardiac Surgery Audit

NICOR: National Institute of Cardiovascular Outcomes Research

ONS: Office for National Statistics

BMI: body mass index

AF: atrial fibrillation

COPD: chronic obstructive pulmonary disease

SSI: Surgical Site Infection

Introduction

Female sex is reported as a risk factor for mortality and morbidity during and after cardiac surgery (1). Whilst advancements in technology and peri-operative care have improved cardiac surgery mortality overall, risk prediction models such as Society of Thoracic Surgeons and Euroscore II, still confer additional operative risk to female patients (2).

Many explanations for this increased peri-operative risk have been postulated. Firstly, women tend to present later in their disease process and have poorer pre-operative baseline risk profiles than males (3). Secondly, female anatomy is reported to be operatively more challenging with smaller, tortuous coronary arteries and smaller diameter cardiac valves (4,5).

A meta-analysis previously published by our group showed females were at a higher risk of mortality and post-operative stroke than males following cardiac surgery (6). However, findings from observational national datasets are conflicting with some studies reporting an increased mortality risk for females (7-9) whilst others report no sex-related differences in mortality following cardiac surgery (10-12). To date, there has not been a sex-specific analysis of contemporary practice of a national outcome dataset from the UK.

The aim of this study was to determine the differences in outcomes between females and males after coronary revascularisation and valvular cardiac surgery within the UK's current practice. The primary outcome was short-term (30-day) mortality. Secondary outcomes included short-term complications such as stroke, sternal wound infection, re-operation for bleeding and length of hospital stay.

Materials and Methods

A complete extract of prospectively collected data from the National Adult Cardiac Surgery Audit (NACSA) was obtained from the National Institute of Cardiovascular Outcomes Research (NICOR) central cardiac database and retrospectively analysed. The definitions of the database variables used for this study are available at https://www.nicor.org.uk/national-cardiac-audit-programme/adult-cardiac-surgery-surgery-audit/. The NICOR registry prospectively collects demographic, as well as pre- and post-operative clinical information, including mortality, for all major adult cardiac surgery procedures performed in the UK. The flow of the data from surgeon-input to analysis has been described elsewhere (13). Briefly, data entered locally by surgeons are validated at the unit-level by database managers prior to upload via a web-portal to NICOR. At this stage, further validation is performed according to logical rules and missing data reports are generated for primary variables (e.g., EuroSCORE risk factors, patient identifiers and outcome data). The data are then forwarded to an academic healthcare informatics department for data cleaning. The complete data cleaning process has been previously described (13). Duplicate records are removed, transcriptional discrepancies re-coded and clinical and temporal conflicts resolved. Missing data are resolved during the validation stages of the data transfer from individual centres. Missing and conflicting data for in-hospital mortality status are backfilled and validated via record linkage to the Office for National Statistics (ONS) census database. The overall percentage of missing data for baseline information is very low (1.7%). Missing categorical or dichotomous variable data were imputed with the mode while missing continuous variables data imputed with the median.

For this study, we used the NACSA dataset study all adult patients who underwent cardiac surgery between 2010-2018. We included elective and urgent isolated coronary revascularization and valvular procedures (aortic valve replacement, mitral valve replacement/repair). We excluded minor procedures, aortic arch surgery, heart transplantation and emergency and salvage surgery.

Statistical Analysis

A Shapiro-Wilks test was used to assess normality of distribution of continuous data. Data of normal distribution was averaged as a mean with standard deviation (SD) and analysed using student t-test. Non-normally distributed data was averaged as a median with interquartile range (IQR) and analysed using a rank sum test. Categorical data is presented as frequencies and compared using a Chi-squared test. For binary outcomes, a logistical regression model was used. For continuous outcomes, a linear regression model was used. Multivariable analysis was used to assess relationships between sex and our outcomes, adjusting for baseline characteristics including age, body mass index (BMI), smoking status, diabetes, chronic obstructive pulmonary disease (COPD), renal failure, cerebrovascular disease, peripheral vascular disease, atrial fibrillation (AF) and hypertension. P-value <0.05 was considered significant in all the analysis. Statistical analysis was performed using R version 4.0.0 using the packages sjplot, lme4, lmertest, gtsummary, ggplot2.

Results

Patient characteristics

CABG and AVR were more commonly performed in males than females whereas more females underwent MVR than males (figure 1 shows the proportion of each intervention per sex).

CABG

During the study period, 121,319 males (82.3%) and 26,157 females (17.7%) underwent an elective or urgent isolated CABG (see table 1). Females tended to be older with more comorbidities such as diabetes, COPD and hypertension. Females were more likely than males to have an urgent rather than elective CABG and females scored more highly in NYHA and CCS scoring systems. Females had shorter cross clamp times and cardio-pulmonary bypass (CPB) times (see table 2). Male were more likely to receive internal mammary artery grafts including left internal mammary artery (LIMA), right internal mammary artery (RIMA) or bilateral internal mammary arteries (BIMA) than females, however, a higher proportion of females received total arterial grafts than males.

Table 1: Baseline characteristics of patients undergoing CABG, females compared to males

Characteristic	**Male**, N = 121,319[1]	**Female**, N = 26,157[1]	**p-value**[2]
Age (years)	67 (60, 74)	70 (62, 76)	<0.001
Body Mass Index (BMI)	28.0 (25.8, 31.2)	28.0 (25.2, 32.0)	0.11
Smoking			<0.001
Never	39,737 (33%)	12,326 (47%)	
Ex-smoker	66,211 (55%)	10,573 (40%)	
Current	15,371 (13%)	3,258 (12%)	
Chronic Obstructive Pulmonary Disorder (COPD)	13,525 (11%)	3,723 (14%)	<0.001
Cerebrovascular disease			<0.001
None	113,159 (93%)	24,151 (92%)	

Characteristic	**Male**, N = 121,319[1]	**Female**, N = 26,157[1]	**p-value**[2]
Transient Ischaemic Attack (TIA)	4,342 (3.6%)	1,082 (4.1%)	
Stroke with recovery	2,368 (2.0%)	606 (2.3%)	
Stroke with deficit	1,450 (1.2%)	318 (1.2%)	
Peripheral Vascular Disease (PVD)	14,661 (12%)	3,292 (13%)	0.025
Diabetes Mellitus			<0.001
None	85,551 (71%)	17,169 (66%)	
Diet controlled	5,232 (4.3%)	1,128 (4.3%)	
Tablet controlled	21,697 (18%)	4,772 (18%)	
Insulin controlled	8,839 (7.3%)	3,088 (12%)	
Hypertension	91,150 (75%)	20,797 (80%)	<0.001
Creatinine >200mmol/ml	1,782 (1.5%)	319 (1.2%)	0.002
Atrial Fibrillation	4,733 (3.9%)	772 (3.0%)	<0.001
Recent Myocardial Infraction (1 month)	38,460 (32%)	9,019 (34%)	<0.001
Previous Cardiac Surgery	1,688 (1.4%)	265 (1.0%)	<0.001
Previous Percutaneous Coronary Intervention			<0.001
None	102,250 (84%)	22,239 (85%)	
<24 hours, same admission	434 (0.4%)	87 (0.3%)	
>24 hours, same admission	1,613 (1.3%)	394 (1.5%)	
>24 hours, previous admission	17,022 (14%)	3,437 (13%)	
Left Ventricular Ejection Fraction			<0.001
Poor <30%	5,544 (4.6%)	905 (3.5%)	
Moderate 30-50%	28,702 (24%)	5,366 (21%)	
Good [?]50%	87,073 (72%)	19,886 (76%)	
New York Heart Association Score			<0.001
1	35,885 (30%)	5,989 (23%)	
2	59,911 (49%)	12,732 (49%)	
3	22,783 (19%)	6,533 (25%)	
4	2,740 (2.3%)	903 (3.5%)	
Canadian Cardiovascular Society Score			<0.001
0	12,606 (10%)	2,318 (8.9%)	
1	11,369 (9.4%)	1,994 (7.6%)	
2	47,198 (39%)	9,233 (35%)	
3	35,695 (29%)	8,443 (32%)	
4	14,451 (12%)	4,169 (16%)	
Euroscore II Score	1.60 (1.17, 2.35)	2.11 (1.46, 3.15)	<0.001
Urgency			<0.001
Elective	71,235 (59%)	13,890 (53%)	
Urgent	50,084 (41%)	12,267 (47%)	

Characteristic	**Male**, N = 121,319[1]	**Female**, N = 26,157[1]	**p-value**[2]
[1] Median (IQR); n (%) [2] Wilcoxon rank sum test; Pearson's Chi-squared test	[1] Median (IQR); n (%) [2] Wilcoxon rank sum test; Pearson's Chi-squared test	[1] Median (IQR); n (%) [2] Wilcoxon rank sum test; Pearson's Chi-squared test	[1] Median (IQR); n (%) [2] Wilcoxon rank sum test; Pearson's Chi-squared test

Table 2: Operative characteristics of CABG

Characteristic	**Male**, N = 121,319[1]	**Female**, N = 26,157[1]	**p-value**[2]
Use of Cardiopulmonary Bypass	100,140 (86%)	21,383 (85%)	<0.001
Aortic Cross Clamp Time (mins)	52 (37, 62)	48 (34, 62)	<0.001
Cardiopulmonary Bypass Time (mins)	82 (62, 103)	78 (58, 98)	<0.001
Use of Left Internal Mammary Artery	110,028 (91%)	23,004 (88%)	<0.001
Use of Bilateral Internal Mammary Arteries	6,532 (5.4%)	820 (3.1%)	<0.001
Use of Right Internal Mammary Artery	7,226 (6.0%)	1,025 (3.9%)	<0.001
Use of Radial Artery	8,269 (6.8%)	1,621 (6.2%)	<0.001
Vein grafts			<0.001
Short saphenous	18,885 (16%)	4,531 (17%)	
Long saphenous	101,909 (84%)	21,523 (82%)	
Other vein	525 (0.4%)	103 (0.4%)	
Total arterial grafts	15,040 (12%)	3,716 (14%)	<0.001
Number of grafts	3.00 (2.00, 4.00)	3.00 (2.00, 3.00)	<0.001
[1] n (%); Median (IQR) [2] Pearson's Chi-squared test; Wilcoxon rank sum test	[1] n (%); Median (IQR) [2] Pearson's Chi-squared test; Wilcoxon rank sum test	[1] n (%); Median (IQR) [2] Pearson's Chi-squared test; Wilcoxon rank sum test	[1] n (%); Median (IQR) [2] Pearson's Chi-squared test; Wilcoxon rank sum test

AVR

26,742 males (58.3%) and 19,168 females (41.7%) underwent an elective or urgent isolated AVR (see table 3). Females tended to be older but were more likely to have an elective rather than urgent AVR compared to males (see supplementary table 1).

Females had shorter cross clamp times and CPB times than males. Biological aortic valves were most commonly implanted in both males and females but males were more likely to receive a mechanical implant or autologous graft than females.

Table 3: Baseline characteristics of patients undergoing AVR, females compared to males

Characteristic	**Male**, N = 26,742[1]	**Female**, N = 19,168[1]	**p-value**[2]
Age (years)	70 (62, 77)	74 (67, 79)	<0.001
Body Mass Index (BMI)	27.9 (25.2, 31.1)	27.9 (24.6, 32.5)	<0.001

Characteristic	**Male**, N = 26,742[1]	**Female**, N = 19,168[1]	**p-value**[2]
Smoking			<0.001
Never	10,757 (40%)	11,195 (58%)	
Ex-smoker	13,853 (52%)	6,704 (35%)	
Current	2,132 (8.0%)	1,269 (6.6%)	
Chronic Obstructive Pulmonary Disorder (COPD)	3,512 (13%)	2,981 (16%)	<0.001
Cerebrovascular disease			<0.001
None	24,149 (90%)	17,501 (91%)	
Transient Ischaemic Attack (TIA)	1,306 (4.9%)	959 (5.0%)	
Stroke with recovery	751 (2.8%)	457 (2.4%)	
Stroke with deficit	536 (2.0%)	251 (1.3%)	
Peripheral Vascular Disease (PVD)	2,070 (7.7%)	1,138 (5.9%)	<0.001
Diabetes Mellitus			0.004
None	21,916 (82%)	15,756 (82%)	
Diet controlled	939 (3.5%)	727 (3.8%)	
Tablet controlled	3,026 (11%)	2,005 (10%)	
Insulin controlled	861 (3.2%)	680 (3.5%)	
Hypertension	16,918 (63%)	12,420 (65%)	<0.001
Creatinine >200mmol/ml	676 (2.5%)	195 (1.0%)	<0.001
Atrial Fibrillation	3,802 (14%)	2,490 (13%)	<0.001
Recent Myocardial Infraction (1 month)	549 (2.1%)	322 (1.7%)	0.004
Previous Cardiac Surgery	2,796 (10%)	1,332 (6.9%)	<0.001
Previous Percutaneous Coronary Intervention			<0.001
None	25,192 (94%)	18,495 (96%)	
<24 hours, same admission	40 (0.1%)	33 (0.2%)	
>24 hours, same admission	38 (0.1%)	26 (0.1%)	
>24 hours, previous admission	1,472 (5.5%)	614 (3.2%)	
Left Ventricular Ejection Fraction			<0.001
Poor <30%	1,632 (6.1%)	628 (3.3%)	
Moderate 30-50%	5,386 (20%)	2,654 (14%)	
Good [?]50%	19,724 (74%)	15,886 (83%)	
New York Heart Association Score			<0.001
1	3,867 (14%)	1,753 (9.1%)	
2	10,929 (41%)	7,115 (37%)	
3	10,132 (38%)	8,907 (46%)	
4	1,814 (6.8%)	1,393 (7.3%)	
Canadian Cardiovascular Society Score			0.024
0	16,210 (61%)	11,453 (60%)	
1	3,423 (13%)	2,449 (13%)	

Characteristic	**Male**, N = 26,742[1]	**Female**, N = 19,168[1]	**p-value**[2]
2	5,053 (19%)	3,651 (19%)	
3	1,659 (6.2%)	1,333 (7.0%)	
4	397 (1.5%)	282 (1.5%)	
Euroscore II Score	1.67 (1.17, 2.71)	1.99 (1.38, 3.07)	<0.001
Urgency			<0.001
Elective	20,715 (77%)	15,649 (82%)	
Urgent	6,027 (23%)	3,519 (18%)	
[1] Median (IQR); n (%)	[1] Median (IQR); n (%)	[1] Median (IQR); n (%)	[1] Median (IQR); n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test	[2] Wilcoxon rank sum test; Pearson's Chi-squared test	[2] Wilcoxon rank sum test; Pearson's Chi-squared test	[2] Wilcoxon rank sum test; Pearson's Chi-squared test

MVR

7,991 males (47.7%) and 8,778 females (52.3%) underwent an elective or urgent isolated MVR (see table 4). Females were more likely to have an elective rather than urgent MVR compared to males. Females tended to be older with higher rates of COPD and diabetes.

Females had shorter cross clamp times and CPB times than males. Males were more likely than females to have a MV repair rather than a MV replacement (see supplementary table 2).

Table 4: Baseline characteristics of patients undergoing MVR, females compared to males

Characteristic	**Male**, N = 7,991[1]	**Female**, N = 8,778[1]	**p-value**[2]
Age (years)	68 (59, 75)	69 (58, 76)	<0.001
Body Mass Index (BMI)	26.5 (23.7, 29.1)	26.6 (23.1, 30.3)	0.037
Smoking			<0.001
Never	3,378 (42%)	4,866 (55%)	
Ex-smoker	3,858 (48%)	2,979 (34%)	
Current	755 (9.4%)	933 (11%)	
Chronic Obstructive Pulmonary Disorder (COPD)	1,071 (13%)	1,620 (18%)	<0.001
Cerebrovascular disease			<0.001
None	7,170 (90%)	7,696 (88%)	
Transient Ischaemic Attack (TIA)	345 (4.3%)	501 (5.7%)	
Stroke with recovery	257 (3.2%)	340 (3.9%)	
Stroke with deficit	219 (2.7%)	241 (2.7%)	
Peripheral Vascular Disease (PVD)	575 (7.2%)	473 (5.4%)	<0.001
Diabetes Mellitus			0.009
None	6,956 (87%)	7,496 (85%)	
Diet controlled	212 (2.7%)	287 (3.3%)	
Tablet controlled	616 (7.7%)	726 (8.3%)	
Insulin controlled	207 (2.6%)	269 (3.1%)	
Hypertension	4,342 (54%)	4,586 (52%)	0.007
Creatinine >200mmol/ml	318 (4.0%)	173 (2.0%)	<0.001
Atrial Fibrillation	2,865 (36%)	3,745 (43%)	<0.001

Characteristic	**Male**, N = 7,991[1]	**Female**, N = 8,778[1]	**p-value**[2]
Recent Myocardial Infraction (1 month)	383 (4.8%)	272 (3.1%)	<0.001
Previous Cardiac Surgery	1,555 (19%)	1,412 (16%)	<0.001
Previous Percutaneous Coronary Intervention			0.020
None	7,543 (94%)	8,373 (95%)	
<24 hours, same admission	9 (0.1%)	12 (0.1%)	
>24 hours, same admission	32 (0.4%)	24 (0.3%)	
>24 hours, previous admission	407 (5.1%)	369 (4.2%)	
Left Ventricular Ejection Fraction			<0.001
Poor <30%	537 (6.7%)	299 (3.4%)	
Moderate 30-50%	2,523 (32%)	2,155 (25%)	
Good [?]50%	4,931 (62%)	6,324 (72%)	
New York Heart Association Score			<0.001
1	923 (12%)	519 (5.9%)	
2	2,662 (33%)	2,408 (27%)	
3	3,393 (42%)	4,693 (53%)	
4	1,013 (13%)	1,158 (13%)	
Canadian Cardiovascular Society Score			0.2
0	5,404 (68%)	6,044 (69%)	
1	956 (12%)	1,066 (12%)	
2	1,052 (13%)	1,066 (12%)	
3	411 (5.1%)	431 (4.9%)	
4	168 (2.1%)	171 (1.9%)	
Euroscore II Score	2.32 (1.45, 4.13)	2.52 (1.60, 4.29)	<0.001
Urgency			<0.001
Elective	5,572 (70%)	6,834 (78%)	
Urgent	2,419 (30%)	1,944 (22%)	
[1] Median (IQR); n (%) [2] Wilcoxon rank sum test; Pearson's Chi-squared test	[1] Median (IQR); n (%) [2] Wilcoxon rank sum test; Pearson's Chi-squared test	[1] Median (IQR); n (%) [2] Wilcoxon rank sum test; Pearson's Chi-squared test	[1] Median (IQR); n (%) [2] Wilcoxon rank sum test; Pearson's Chi-squared test

Outcomes

The rate of 30-day mortality by procedure and within each sex stratum is presented in Figure 2.

Figure 3 shows 30-day mortality by procedure and sex over time.

CABG

Females, compared to males, had greater odds of experiencing 30-day mortality after CABG (OR 1.76, CI 1.47-2.09, $p<0.001$) (see table 5). Females also experienced increased need for post-operative dialysis (OR 1.31, CI 1.12-1.52, $p<0.001$), deep sternal wound infections (OR 1.43, CI 1.11-1.83, $p=0.005$) and length of stay (Beta 1.2, CI 1.0-1.4, $p<0.001$) compared to males. However, female sex was protective against returning to theatre for post-operative bleeding (OR 0.76, CI 0.65-0.87, p<0.001). There was no sex-related difference in post-operative cerebrovascular accident (CVA) following CABG (OR 1.01, CI 0.79-1.28, p>0.9).

Table 5: Multivariable regression analysis of outcomes following CABG, females compared to males

Outcome	**Males** N = 121,3191	**Females** N = 26,1571	**Adjusted OR**	**95% CI**	**p-value**
Mortality	1,302 (1.1%)	496 (1.9%)	1.76	1.47-2.09	<0.001
Post-operative Cerebrovascular Accident			1.01	0.79, 1.28	>0.9
Transient Ischaemic Attack	397(0.4%)	102 (0.4%)			
Stroke	558 (0.5%)	154 (0.7%)			
Return To Theatre for Bleeding	3,389 (2.8%)	619 (2.4%)	0.76	0.65, 0.87	<0.001
Post-operative dialysis	1,933 (1.7%)	574 (2.4%)	1.31	1.12, 1.52	<0.001
Deep Sternal Surgical Site Infection	695 (0.9%)	209 (1.3%)	1.43	1.11, 1.83	0.005
Hospital Length of Stay	8 (6, 13)	9 (7, 15)	1.2	1.0, 1.4	<0.001

AVR

Following AVR, females had a greater odds of 30-day mortality compared to males (OR 1.59, CI 1.27-1.99, p<0.001) (see table 6). Female sex was protective against returning to theatre for post-operative bleeding (OR 0.72, CI 0.61-0.84, p<0.001) and deep sternal wound infections l SSI (OR 0.60, CI 0.33-1.03, p=0.074). There were no significant gender-related differences in outcomes of post-operative CVA (OR 1.03, CI 0.78-1.36, p=0.8), post-operative dialysis (OR 0.94, CI 0.76-1.15, p=0.5) and in hospital length of stay (beta 0.2, CI -0.20-0.60, p=0.3).

Table 6: Multivariable regression analysis of outcomes following AVR, females compared to males

Outcome	**Males** N = 26,7421	**Females N = 19,1681**	**OR**	**95% CI**	**p-value**
Mortality	525 (2.0%)	521 (2.7%)	1.59	1.27, 1.99	<0.001
Post-operative Cerebrovascular Accident			1.03	0.78, 1.36	0.8
Transient Ischaemic Attack	180 (0.8%)	133 (0.8%)			
Stroke	224 (0.9%)	175 (1.0%)			
Return To Theatre for Bleeding	1,362 (5.1%)	681 (3.6%)	0.72	0.61, 0.84	<0.001

Outcome	**Males** N = 26,7421	**Females N = 19,1681**	**OR**	**95% CI**	**p-value**
Post-operative dialysis	745 (3.1%)	487 (2.8%)	0.94	0.76, 1.15	0.5
Deep Sternal Surgical Site Infection	108 (0.6%)	61 (0.5%)	0.60	0.33, 1.03	0.074
Hospital Length of Stay	9 (7, 14)	9 (7, 15)	0.20	-0.20, 0.60	0.3

MVR

Females had a greater odds of 30-day mortality after MVR compared to males (OR 1.37, CI 1.09-1.71, p=0.006) (see table 7). However, females had less deep sternal wound infections (OR 0.56, CI 0.29-1.05, p=0.076) and a reduced hospital LOS (beta -1.6, CI -2.5- -0.63, p<0.001) compared to males. There were no significant differences between males and females for outcomes of post-operative CVA (OR 1.00, CI 0.71-1.43, p>0.9), returning to theatre for post-operative bleeding (OR 0.87, CI 0.70-1.08, p=0.2) and post-operative dialysis (OR 0.88, CI 0.71-1.09, p=0.3).

Table 7: Multivariable regression analysis of outcomes following MVR, females compared to males

Outcome	**Males** N = 7,9911	**Females** N = 8,7781	**OR**	**95% CI**	**p-value**
Mortality	456 (5.8%)	546 (6.3%)	1.37	1.09, 1.71	0.006
Post-operative Cerebrovascular Accident			1.00	0.71, 1.43	>0.9
Transient Ischaemic Attack	75 (1.0%)	86 (1.1%)			
Stroke	123 (1.7%)	116 (1.5%)			
Return To Theatre for Bleeding	550 (6.9%)	480 (5.5%)	0.87	0.70, 1.08	0.2
Post-operative dialysis	513 (7.0%)	489 (6.1%)	0.88	0.71, 1.09	0.3
Deep Sternal Surgical Site Infection	54 (1.2%)	45 (0.9%)	0.56	0.29, 1.05	0.076
Hospital Length of Stay	12 (8, 22)	12 (9, 20)	-1.6	-2.5, -0.63	0.001

Discussion

This study is the first to review current practice of UK national data to compare sex-related differences in outcomes following surgical coronary revascularisation and valvular cardiac procedures.

From our dataset of 210,155 patients (25.7% female), we found female sex to be an important risk factor for 30 day mortality following CABG, AVR and MVR. Following CABG, female sex was also associated with increased post-operative need for dialysis, deep sternal wound infections and length of hospital stay.

The present study supports the well reported claim that females undergoing coronary revascularisation surgery are often older and with more comorbidities than males (3). Furthermore, we found that women were also more likely to need urgent, as opposed to elective, revascularisation than men, which may be responsible for some of the poorer outcomes reported.

It is also suggested that sex-related differences in operative strategy decisions and techniques may explain sex-related differences in cardiac surgery outcomes (14). For example, a higher proportion of males compared with females received LIMA, RIMA or BIMA grafting in both our cohort and other studies (15) which is suggested to predispose females to incomplete myocardial revascularisation (16,17). Nevertheless, the multivariable regression analysis used in our study adjusted for differences in baseline and operative differences, including revascularisation strategy and still a sex-related difference remained in short-term mortality. These findings suggest that female sex is an independent risk factor for short-term mortality following CABG which supports the consensus of the current literature (6,18). The idea of female sex being an independent risk factor for worse outcomes following CABG is speculated to be related to the more challenging anatomy of female patients, such as smaller coronary artery targets for grafting, narrower conduits and more diffuse patterns of coronary disease (3,19).

Our study also evaluated other post-CABG outcomes. We did not find an increased risk of stroke following CABG as other national studies have reported (8, 20). This may be related to the fact that in our cohort of females a significant 15% underwent off pump revascularisation which has been reported to be particularly beneficial in women because of its effect to reduce the risk of stroke (21).

Sternal wound complications were more common in females than males following CABG in our study. A risk prediction tool developed in the UK identifies female sex as one of six independent predictors of surgical site infection following cardiac surgery (22). The B-SIR score also includes raised body mass index >30, diabetes, left ventricular ejection fraction <45% and peripheral vascular disease; all of which were more common in our female patients. This finding may indicate a complex multifactorial impact of female sex on the risk of developing wound complications. This would suggest that efforts to prevent SSI should aim to target all of the these modifiable risk factors, especially in our female patients.

While the majority of patients who underwent CABG were male, single valve surgery was more evenly distributed between the sexes. In contrast to CABG, females were more likely to have a planned elective valve procedure. Despite this, female sex was associated with significantly higher short-term mortality following both isolated AVR and MVR procedures.

Our finding of increased mortality following AVR in females is reflected from other nationally representative databases such as United States of America (23) and a previous UK database analysis (24). However, other national studies did not report sex-related differences in AVR mortality (12, 25).

In our study, men were more likely to receive a mechanical aortic valve than women which may reflect the differences in age and comorbidities between the sexes at time of surgery and their influence on the management planning. It is known that women with severe aortic stenosis are diagnosed at a later stage of the disease process (26) but even when adjusting for pre-operative difference women are less likely to be referred for surgical AVR than men (27, 28).

There is no clear explanation for why women have worse outcomes compared to men following AVR but several mechanisms have been implicated. For similar degrees of aortic stenosis, females tend to have higher transvalvular pressure gradients, thicker ventricle walls and smaller end-systolic and end-diastolic chamber sizes than males (29). Secondly, females on average receive smaller valves than males, the outcomes of patient-prosthesis mismatch (PPM) seem more severe in smaller size valves (30) and therefore may effect women disproportionately. Furthermore, females are also more likely to require additional aortic annular enlargement than males leading to increased operative risk associated with the annular enlargement procedure (5).

As with the other procedures, females in the UK experienced an increased odds of 30-day mortality following

MVR than males. A 2013 study of 3,761 patients found a difference in mitral pathology between males and females undergoing mitral surgery; males were more likely to have mitral valve leaflet prolapse whereas females were more likely to have calcified mitral valve leaflets (31). This differences in pathology explains why females are more likely to need a mitral valve replacement whilst males are more likely to receive a mitral valve repair, a finding reiterated in our study. A study of MV procedures from USA, 2000-2009, also agreed men were more likely to receive a MV repair than women (32). This difference in surgical management strategy is thought to contribute to the poorer outcomes we see in females (33).

Interestingly, for both CABG and AVR surgery, female sex seemed to be protective for post-operative bleeding resulting in returning to theatre. Oestrogen has a pro-coagulant effect which may confer benefit to limit post-operative bleeding (35). Despite females tending to have lower rates of returning to theatre for bleeding, females have been shown to receive more post-operative red blood cell transfusions with males and this is associated with delayed recovery (10).

Limitations

The present study has several limitations. Firstly, we are limited to short-term outcomes without long-term follow-up. While, 30-day outcomes following cardiac surgery are important for evaluation of safety and efficiency, this data only forms part of the story. It is often reported than sex ceases to be an independent determinant of outcomes following cardiac surgery in a long-term follow-up (34) and it is important to know if this pattern is also reflected in the UK population and healthcare system. Secondly, this study used data from NACSA database and therefore we were limited to analysing data collected for this purpose.

Lastly, by the nature of being an observational non-randomised cohort, despite adjusting for known confounders, the effect of unknown confounders remains.

Conclusion

Despite advances in cardiac surgery, females in the UK have an increased risk of short-term mortality after cardiac surgery compared to males. This highlights the need to focus on the understanding of the causes behind these disparities, followed by implementation of sex-specific strategies to improve the outcomes of females undergoing cardiac surgery.

Contributorship statement:

Lauren Kari Dixon: Conceptualization, methodology, software, formal analysis, writing – original draft, writing - Review & Editing

Arnaldo Dimagli: Conceptualization, methodology, software, formal analysis, writing - Review & Editing

Ettorino Di Tommaso: Conceptualization, formal analysis, writing - Review & Editing

Shubhra Sinha: Conceptualization, software, formal analysis, writing - Review & Editing

Daniel Paul Fudulu: Writing - Review & Editing

Manraj Sandhu: Writing - Review & Editing

Umberto Benedetto: Conceptualization, methodology, supervision

Gianni Angelini: Conceptualization, methodology, writing - Review & Editing, supervision

Competing interests: None

Funding statement: This study was supported by the British Heart Foundation and NIHR Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol.

Data Availability statement : All data relevant to the study are included in the article or uploaded as supplementary information. No additional data is available.

Ethical approval: All the analysed data was anonymised; hence there was no need to obtain further ethics approval.

Transparency statement : The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Figures

Figure 1: Percentage of procedure AVR, CABG and MVR by sex

Figure 2: Percentage mortality of each sex by procedure AVR, CABG and MVR

Figure 3: Percentage mortality of each sex by procedure AVR, CABG and MVR over time

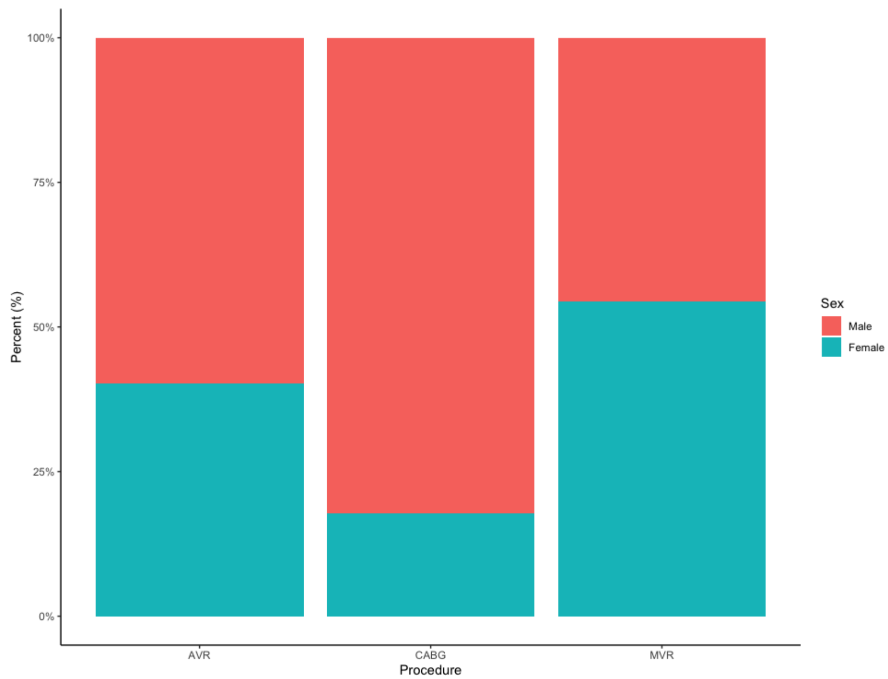

Figure 1: Percentage of procedure AVR, CABG and MVR by sex

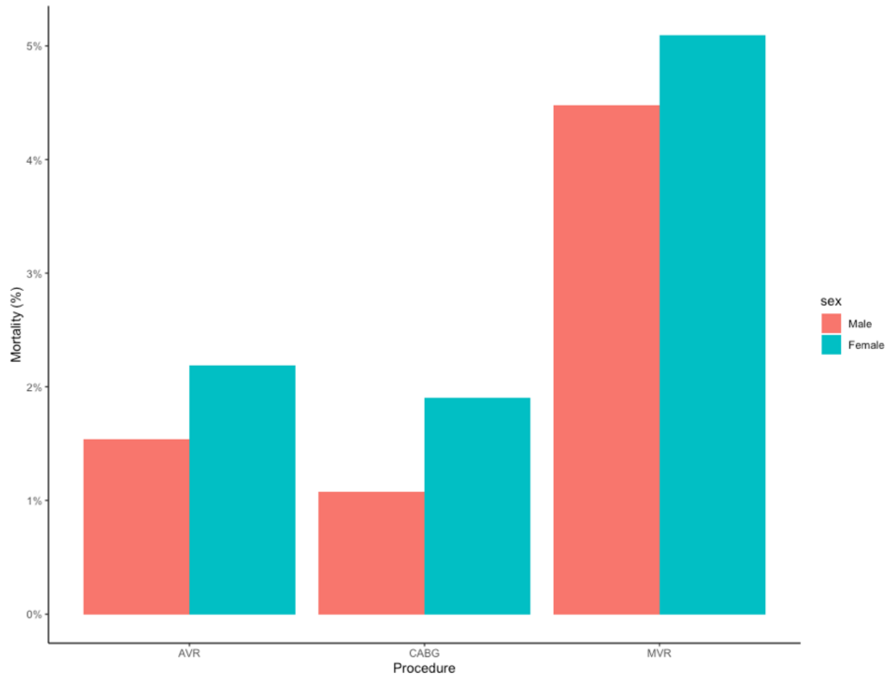

Figure 2: Percentage mortality of each sex by procedure AVR, CABG and MVR

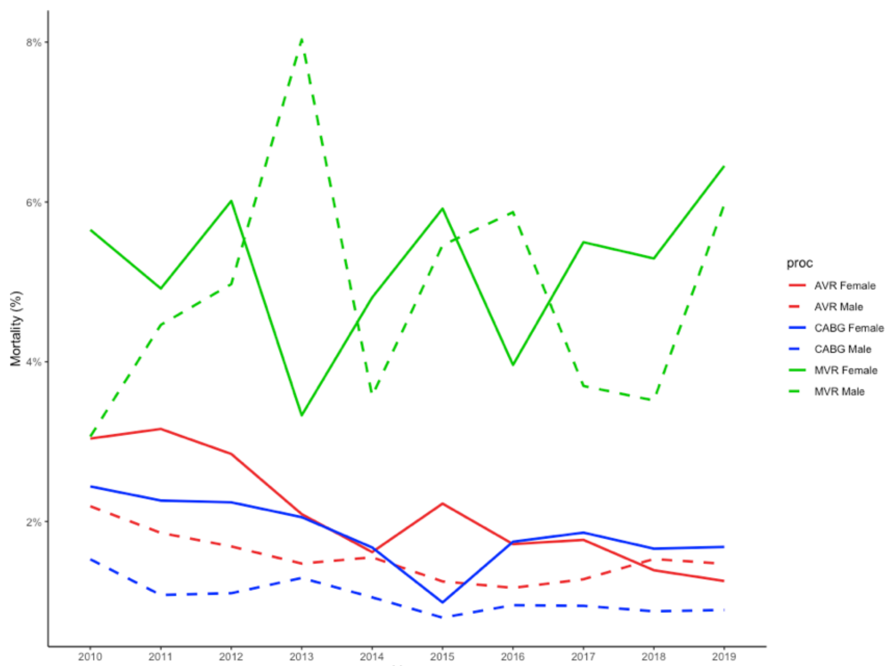

Figure 3: Percentage mortality of each sex by procedure AVR, CABG and MVR over time

References

1. Samer A.M. Nashef, François Roques, Linda D. Sharples, Johan Nilsson, Christopher Smith, Antony

R. Goldstone, Ulf Lockowandt, EuroSCORE II, European Journal of Cardio-Thoracic Surgery, Volume 41, Issue 4, April 2012, Pages 734–745, https://doi.org/10.1093/ejcts/ezs043

2. Prins C, de Villiers Jonker I, Botes L, Smit FE. Cardiac surgery risk-stratification models. *Cardiovasc J Afr* . 2012;23(3):160-164. doi:10.5830/CVJA-2011-047
3. A. Haider, S. Bengs, J. Luu, E. Osto, J.M. Siller-Matula, T. Muka, C. Gebhard, Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome, Eur. Heart J. 41 (13) (2020 Apr 1) 1328–1336, https://doi. org/10.1093/eurheartj/ehz898 (PMID: 31876924).
4. R.Blankstein, R.P.Ward, M.Arnsdorf, B.Jones, Y.B.Lou, M.Pine, Female gender is an independent predictor of operative mortality after coronary artery bypass graft surgery: contemporary analysis of 31 Midwestern hospitals, Circulation 112 (9 Suppl) (2005 Aug 30) I323–I327, https://doi.org/10.1161/ CIRCULATIONAHA.104.525139. 16159840.
5. E.H. Blackstone, D.M. Cosgrove, W.R. Jamieson, et al., Prosthesis size and long- term survival after aortic valve replacement, J. Thorac. Cardiovasc. Surg. 126 (2003) 783–796.
6. L.K. Dixon, E.Di Tommaso, A.Dimagli, S.Sinha, M.Sandhu, U.Benedetto, G.D.Angelini, Impact of sex on outcomes after cardiac surgery: A systematic review and meta-analysis, International Journal of Cardiology, 2021, ISSN 0167-5273, https://doi.org/10.1016/j.ijcard.2021.09.011.
7. M. Dalen, S. Nielsen, T. Ivert, M.J. Holzmann, U. Sartipy, Coronary artery bypass grafting in women 50 years or younger, J. Am. Heart Assoc. 8 (18) (2019 Sep 17), e013211, https://doi.org/10.1161/JAHA.119.013211 (Epub 2019 Sep 14. PMID: 31522591; PMCID: PMC6818006).
8. Swaminathan RV, Feldman DN, Pashun RA, Patil RK, Shah T, Geleris JD, Wong SC, Girardi LN, Gaudino M, Minutello RM, Singh HS, Bergman G, Kim LK, Gender Differences in In-Hospital Outcomes After Coronary Artery Bypass Grafting, The American Journal of Cardiology (2016), doi: 10.1016/j.amjcard.2016.05.004.
9. A. Maraschini, F. Seccareccia, P. D'Errigo, S. Rosato, G. Badoni, G. Casali,F. Musumeci, Role of gender and age on early mortality after coronary artery bypass graft in different hospitals: data from a national administrative database, Interact. Cardiovasc. Thorac. Surg. 11 (5) (2010 Nov) 537–542, https://doi.org/ 10.1510/icvts.2010.233296 (Epub 2010 Aug 13. PMID: 20709699).
10. A. Saxena, D. Dinh, J.A. Smith, G. Shardey, C.M. Reid, A.E. Newcomb, Sex differences in outcomes following isolated coronary artery bypass graft surgery in Australian patients: analysis of the Australasian Society of Cardiac and Thoracic Surgeons cardiac surgery database, Eur. J. Cardiothorac. Surg. 41 (4) (2012 Apr) 755–762, https://doi.org/10.1093/ejcts/ezr039 (Epub 2011 Nov 11. PMID: 22423056).
11. A. Saxena, C.L. Poh, D.T. Dinh, C.M. Reid, J.A. Smith, G.C. Shardey, A.E. Newcomb, Does patient gender affect outcomes after concomitant coronary artery bypass graft and aortic valve replacement? An Australian Society of Cardiac and Thoracic Surgeons Database study, Cardiology 119 (2) (2011) 116–123, https://doi.org/10.1159/000330133 (Epub 2011 Sep 9. PMID: 21912125).
12. K. Kaier, Mühlen C. von Zur, A. Zirlik, C. Schmoor, K. Roth, W. Bothe, P. Hehn, J. Reino hl, M. Zehender, C. Bode, P. Stachon, Sex-specific differences in outcome of transcatheter or surgical aortic valve replacement, Can. J. Cardiol. 34 (8) (2018 Aug) 992–998, https://doi.org/10.1016/j.cjca.2018.04.009 (Epub 2018 Apr 12. PMID: 30056851).
13. Hickey GL, Grant SW, Cosgriff R, Dimarakis I, Pagano D, Kappetein AP, et al. Clinical registries: governance, management, analysis and applications. Eur J cardio-thoracic Surg Off J Eur Assoc Cardio-thoracic Surg. 2013 Oct;44(4):605–14.
14. C.G. Koch, Y.S. Weng, S.X. Zhou, J.S. Savino, J.P. Mathew, P.H. Hsu, L.J. Saidman, D.T. Mangano, Ischemia Research and Education Foundation, Multicenter Study of Perioperative Ischemia Research Group, Prevalence of risk factors, and not gender per se, determines short- and long-term survival after coronary artery bypass surgery, J. Cardiothorac. Vasc. Anesth. 17 (5) (2003 Oct) 585–593, https://doi. org/10.1016/s1053-0770(03)00201-5 (PMID: 14579211).
15. M. Gaudino, Z. Samadashvili, I. Hameed, J. Chikwe, L.N. Girardi, E.L. Hannan, Differences in long-term outcomes after coronary artery bypass grafting using single vs multiple arterial grafts and the association with sex, JAMA Cardiol. 6 (4) (2021) 401–409, https://doi.org/10.1001/jamacardio.2020.6585.
16. R. Hessian, H. Jabagi, J.M.C. Ngu, F.D. Rubens, Coronary surgery in women and the challenges we

face, Can. J. Cardiol. 34 (4) (2018 Apr) 413–421, https://doi. org/10.1016/j.cjca.2018.01.087 (Epub 2018 Feb 3. PMID: 29571425).

17. S. Oertelt-Prigione, F. Kendel, M. Kaltenbach, R. Hetzer, V. Regitz-Zagrosek, R. Baretti, Detection of gender differences in incomplete revascularization after coronary artery bypass surgery varies with classification technique, Biomed. Res. Int. 2013 (2013) 108475, https://doi.org/10.1155/2013/108475.
18. M. Alam, S.J. Bandeali, W.T. Kayani, W. Ahmad, S.A. Shahzad, H. Jneid, Y. Birnbaum, N.S. Kleiman, J.S. Coselli, C.M. Ballantyne, N. Lakkis, S.S. Virani, Comparison by meta-analysis of mortality after isolated coronary artery bypass grafting in women versus men, Am. J. Cardiol. 112 (3) (2013 Aug 1) 309–317, https://doi.org/10.1016/j.amjcard.2013.03.034. Epub 2013 May 1, 23642381.
19. N.J. O'Connor, J.R. Morton, J.D. Birkmeyer, E.M. Olmstead, G.T. O'Connor, Effect of coronary artery diameter in patients undergoing coronary bypass surgery. Northern New England Cardiovascular Disease Study Group, Circulation 93 (4) (1996 Feb 15) 652–655, https://doi.org/10.1161/01.cir.93.4.652 (PMID: 8640991).
20. W. Mohamed, M.O. Mohamed, S. Hirji, M. Ouzounian, L.Y. Sun, T. Coutinho, E. Percy, M.A. Mamas, Trends in sex-based differences in outcomes following coronary artery bypass grafting in the United States between 2004 and 2015, Int. J. Cardiol. 320 (2020 Dec 1) 42–48, https://doi.org/10.1016/j.ijcard.2020.07.039 (Epub 2020 Jul 29. PMID: 32735897).
21. C. Dominici, A. Salsano, A. Nenna, C. Spadaccio, Z. El-Dean, M. Bashir, G. Mariscalco, F. Santini, M. Chello, Neurological outcomes after on-pump vs off- pump CABG in patients with cerebrovascular disease, J. Card. Surg. 34 (10) (2019 Oct) 941–947, https://doi.org/10.1111/jocs.14158 (Epub 2019 Jul 3. PMID: 31269312).
22. Magboo R, Drey N, Cooper J, Byers H, Shipolini A, Sanders J. Predicting cardiac surgical site infection: development and validation of the Barts Surgical Infection Risk tool. J Clin Epidemiol. 2020 Dec;128:57-65. doi: 10.1016/j.jclinepi.2020.08.015. Epub 2020 Aug 25. PMID: 32853763
23. Astor BC, Kaczmarek RG, Hefflin B, Daley WR. Mortality after aortic valve replacement: results from a nationally representative database. Ann Thorac Surg. 2000 Dec;70(6):1939-45. doi: 10.1016/s0003-4975(00)01670-2. PMID: 11156099.
24. Dunning J, Gao H, Chambers J, Moat N, Murphy G, Pagano D, Ray S, Roxburgh J, Bridgewater B. Aortic valve surgery: marked increases in volume and significant decreases in mechanical valve use–an analysis of 41,227 patients over 5 years from the Society for Cardiothoracic Surgery in Great Britain and Ireland National database. J Thorac Cardiovasc Surg. 2011 Oct;142(4):776-782.e3. doi: 10.1016/j.jtcvs.2011.04.048. PMID: 21924147.
25. M.M. Mokhles, S. Soloukey Tbalvandany, S. Siregar, M.I.M. Versteegh, L. Noyez, B. van Putte, A.B.A. Vonk, J.W. Roos-Hesselink, A.J.J.C. Bogers, J.J.M. Takkenberg, Male-female differences in aortic valve and combined aortic valve/ coronary surgery: a national cohort study in the Netherlands, Open Heart 5 (2) (2018 Sep 10), e000868, https://doi.org/10.1136/openhrt-2018-000868 (PMID: 30228910; PMCID: PMC6135410).
26. Tribouilloy C, Bohbot Y, Rusinaru D, Belkhir K, Diouf M, Altes A, Delpierre Q, Serbout S, Kubala M, Levy F, Maréchaux S, Enriquez Sarano M. Excess Mortality and Undertreatment of Women With Severe Aortic Stenosis. J Am Heart Assoc. 2021 Jan 5;10(1):e018816. doi: 10.1161/JAHA.120.018816. Epub 2020 Dec 29. PMID: 33372529; PMCID: PMC7955469.
27. Bienjonetti-Boudreau D, Fleury MA, Voisine M, Paquin A, Chouinard I, Tailleur M, Duval R, Magnan PO, Beaudoin J, Salaun E, Clavel MA. Impact of sex on the management and outcome of aortic stenosis patients. Eur Heart J. 2021 Jul 15;42(27):2683-2691. doi: 10.1093/eurheartj/ehab242. PMID: 34023890.
28. Chaker Z, Badhwar V, Alqahtani F, Aljohani S, Zack CJ, Holmes DR, Rihal CS, Alkhouli M. Sex Differences in the Utilization and Outcomes of Surgical Aortic Valve Replacement for Severe Aortic Stenosis. J Am Heart Assoc. 2017 Sep 21;6(9):e006370. doi: 10.1161/JAHA.117.006370. PMID: 28935681; PMCID: PMC5634288.
29. Milavetz DL, Hayes SN, Weston SA, Seward JB, Mullany CJ, Roger VL. Sex differences in left ventricular geometry in aortic stenosis: impact on outcome. Chest. 2000 Apr;117(4):1094-9. doi:

10.1378/chest.117.4.1094. PMID: 10767246.

30. Kolkailah AA, Hirji SA, Ejiofor JI, Del Val FR, Chowdhury R, McGurk S, Lee J, Kaneko T. Impact of Prosthesis Size and Prosthesis-Patient Mismatch on Outcomes in Younger Female Patients Undergoing Aortic Valve Replacement. Semin Thorac Cardiovasc Surg. 2020 Summer;32(2):219-228. doi: 10.1053/j.semtcvs.2019.01.005. Epub 2019 Jan 7. PMID: 30630098.
31. Seeburger J, Eifert S, Pfannmüller B, Garbade J, Vollroth M, Misfeld M, Borger M, Mohr FW. Gender differences in mitral valve surgery. Thorac Cardiovasc Surg. 2013 Jan;61(1):42-6. doi: 10.1055/s-0032-1331583. Epub 2012 Dec 20. PMID: 23258762
32. Vassileva CM, Mishkel G, McNeely C, Boley T, Markwell S, Scaife S, Hazelrigg S. Long-term survival of patients undergoing mitral valve repair and replacement: a longitudinal analysis of Medicare fee-for-service beneficiaries. Circulation. 2013 May 7;127(18):1870-6. doi: 10.1161/CIRCULATIONAHA.113.002200. Epub 2013 Apr 8. PMID: 23569153.
33. Vakamudi S, Jellis C, Mick S, Wu Y, Gillinov AM, Mihaljevic T, Cosgrove DM, Svensson L, Cho L. Sex Differences in the Etiology of Surgical Mitral Valve Disease. Circulation. 2018 Oct 16;138(16):1749-1751. doi: 10.1161/CIRCULATIONAHA.118.035789. PMID: 30354470.
34. Nicolini, F., Vezzani, A., Fortuna, D. et al. Gender differences in outcomes following isolated coronary artery bypass grafting: long-term results. J Cardiothorac Surg 11, 144 (2016). https://doi.org/10.1186/s13019-016-0538-4
35. Ambrus JL, Schimert G, Lajos TZ, Ambrus CM, Mink IB, Lassman HB, Moore RH, Melzer J. Effect of antifibrinolytic agents and estrogens on blood loss and blood coagulation factors during open heart surgery. J Med. 1971;2(2):65-81. PMID: 4329735.