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REVIEW

ADULT CARDIAC

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Sex differences in outcomes following coronary artery bypass grafting: a meta-analysis

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Key question

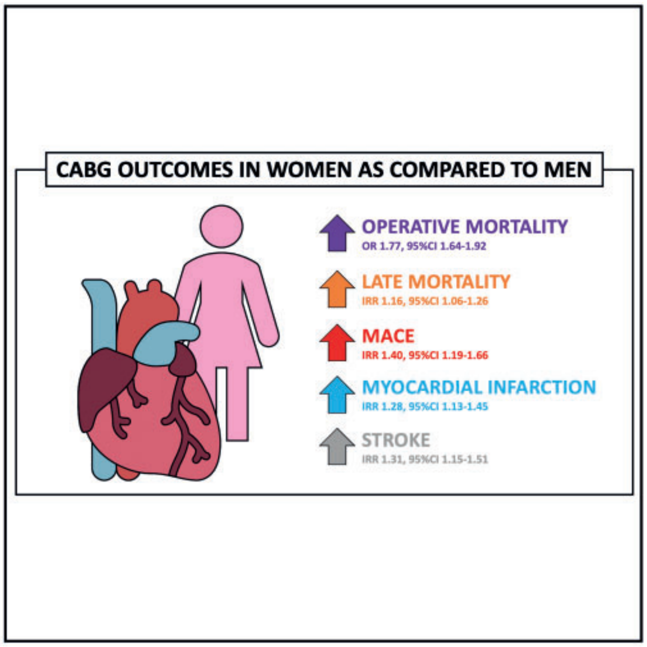
Are there differences in outcomes between the sexes following isolated coronary artery bypass grafting?

Key finding(s)

Women undergoing CABG are at higher risk for late mortality and postoperative events including MACE, MI and stroke.

Take-home message

Outcomes of women undergoing CABG remain suboptimal; studies are needed to elucidate the causes of this difference and improve women's outcomes.



Abstract

OBJECTIVES: Previous reports have found females are a higher risk of morbidity and mortality following isolated coronary artery bypass grafting (CABG). Here, we describe the differences in outcomes following isolated CABG between males and females.

METHODS: Following a systematic literature search, studies reporting sex-related outcomes following isolated CABG were pooled in a meta-analysis performed using the generic inverse variance method. The primary outcome was operative mortality. Secondary outcomes included rates of stroke, repeat revascularization, myocardial infarction, major adverse cardiac events, and late mortality. Subgroup analyses were performed for studies published before and after the year 2000 and for the type of risk adjustment.

RESULTS: Eighty-four studies were included with a total of 903 346 patients. Females were at higher risk for operative mortality (odds ratio: 1.77, 95% confidence interval [CI]: 1.64–1.92, $P < 0.001$). At subgroup analysis, there was no difference in operative or late mortality between studies published prior and after 2000 or between studies using risk adjustment. Females were at a higher risk of late mortality (incidence rate ratio [IRR]: 1.16, 95% CI: 1.06–1.26, $P < 0.001$), major adverse cardiac events (IRR: 1.40, 95% CI: 1.19–1.66, $P < 0.001$), myocardial infarction (IRR: 1.28, 95% CI: 1.13–1.45, $P < 0.001$) and stroke (IRR: 1.31, 95% CI: 1.15–1.51, $P > 0.001$) but not repeat revascularization (IRR: 0.99, 95% CI: 0.76–1.29, $P = 0.95$). The use of the off-pump technique or multiple arterial grafts was not associated with the primary outcome.

CONCLUSIONS: Females undergoing CABG are at higher risk for operative and late mortality as well as postoperative events including major adverse cardiac events, myocardial infarction and stroke.

PROSPERO registration: CRD42020187556

Keywords: Coronary artery bypass grafting • Male • Female • Mortality

INTRODUCTION

The impact of female sex on outcomes following coronary artery bypass grafting (CABG) remains unclear. Previous retrospective analyses have established female sex as an independent predictor of operative mortality [1–3]. Conversely, other analyses have not found a difference in mortality rates between males and females [4–6]. Some studies have identified no difference in mortality, but higher rates of morbidity including renal failure and need for repeat revascularization (RR) among females [6–8].

Most of the published data are limited to retrospective single-series series. The only previously published meta-analysis investigated short- and long-term mortality, and to date, no meta-analytic estimate of the impact of sex on important postoperative events including RR, myocardial infarction (MI), stroke and major adverse cardiac events (MACE) has been published. Furthermore, the prior analysis did not look at predictors of mortality or at the impact of the operative technique on outcomes.

In this analysis, we set out to summarize the impact of sex on operative mortality and other important postoperative outcomes including long-term mortality as well as the effect of patients' characteristics and operative technique on the outcomes.

MATERIALS AND METHODS

This study was registered on PROSPERO, identification number CRD42020187556. No human subjects were involved in this analysis, and ethical approval was not required.

Search strategy

A medical librarian (DW) performed comprehensive searches to identify contemporary randomized trials and observational studies on outcomes following CABG reported by sex. Searches were run on 20 December 2019 in the following databases: Ovid MEDLINE® (ALL; 2008 to present); Ovid EMBASE (1974 to present); and The Cochrane Library (Wiley). The full search strategies are available in Supplementary Material, Table S1.

Study selection and data extraction

Searches across the chosen databases retrieved 9031 results. After results were de-duplicated, 2 independent reviewers (M.M. and A.N.) screened a total of 8734 citations. Discrepancies were resolved by the senior author (M.G.). Titles and abstracts were reviewed against pre-defined inclusion/exclusion criteria. Articles were considered for inclusion if they were written in English, were observational studies or randomized trials reporting sex-specific outcomes following CABG. Animal studies, case reports, conference presentations, editorials, expert opinions, studies reporting outcomes with concomitant surgery and studies not reporting outcomes by sex were excluded.

The full text was pulled for the selected studies for a second round of eligibility screening. Reference lists for articles selected for inclusion in the study were also searched for relevant articles (reverse snowballing). The full Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram outlining the study selection process is available in Supplementary Material, Fig. S1 [9]. All studies were reviewed by 2 independent investigators (M.M. and A.N.) and disagreements were resolved by the senior author (M.G.). For overlapping studies, the largest series were included, but in cases of time overlapping between registries and individual series, the latter were included.

Two investigators (M.M. and A.N.) performed data extraction independently, and the extracted data were verified by a third investigator (M.G.) for accuracy. The following variables were included study data (sample size, publication year, design, institution and country) (Supplementary Material, Table S2), patient demographics (age, sex, comorbidities [diabetes, hypertension, prior MI, hyperlipidaemia, smoking, chronic obstructive pulmonary disease, angina, previous stroke, chronic renal failure and prior percutaneous coronary intervention]), operative mortality rates, long-term mortality rates, and procedural factors (number of grafts, off-pump usage, cardiopulmonary bypass [CPB] time, cross-clamp time, mechanical ventilation time, number of days in the intensive care unit and number of days hospitalized). Full study details are available in Supplementary Material, Tables S3 and S4.

The quality of the included studies was assessed using the Newcastle-Ottawa Scale for observational studies (Supplementary Material, Table S5) [10].

Outcomes and effect summary

The primary outcome was operative mortality. Secondary outcomes included late mortality, as well as long-term MI, stroke, RR and MACE as defined according to the individual study.

Meta-analysis

Short-term binary outcomes were reported as odds ratios (OR) with 95% confidence intervals (CIs) using the generic inverse variance method after extraction of events from the individual studies. For long-term outcomes, the incidence rate ratio (IRR) with its 95% CIs was reported using the generic inverse variance method.

IRR was estimated through several means based on the available study data. When hazard ratios were provided, the natural logarithm of the hazard ratio was used, otherwise, IRR was estimated through the reported events and accumulated group-specific person-years of follow-up. Random effect meta-analysis was performed using 'metafor' and 'meta' packages and publication bias was assessed by funnel plot and Egger's test. Heterogeneity was reported as low (I^2 = 0–25%), moderate (I^2 = 26–50%) or high (I^2 > 50%). Leave-one-out analyses for the primary outcomes were performed to assess the robustness of the obtained estimate.

Subgroup analyses were performed for studies published prior and after the year 2000 and based on the type of risk adjustment used (unadjusted, regression-adjusted and propensity matched).

Meta-regression was used to explore the effects of preoperative variables (age, diabetes, hypertension, previous MI, hyperlipidaemia, smoking, chronic obstructive pulmonary disease, symptomatic angina, stroke, renal failure and prior PCI) as well as intraoperative variables (number of grafts used, off-pump technique and multiple arterial grafting [MAG]) and sex on the primary outcome.

Statistical significance was set at the 2-tailed 0.05 level, without multiplicity adjustments. All statistical analyses were performed using R (version 3.3.3, R Project for Statistical Computing) within RStudio.

RESULTS

Study and patient characteristics

A total of 84 observational studies were included in the final analysis, with a total of 903 346 patients (679 006 males and 224 340 females) (Supplementary Material, Table S2). There were 20 studies published prior to the year 2000, and 64 studies published after the year 2000. Twelve studies were unadjusted, 59 were regression-adjusted and 13 studies utilized propensity matching. Twenty-four were multicentre studies; 17 originated from the USA, 11 from Germany, 7 from Sweden, 5 from Turkey, 4 were multinational, 4 from the UK, 4 from Italy, 4 from the Netherlands, 3 from Japan, 3 from Norway, 3 from Canada, 2 from Austria, 2 from China, 2 from Israel, 2 from Poland, 2 from Korea and 1 each from Australia, Brazil, the Czech Republic, Finland, India, Iran, Pakistan, Saudi Arabia, Switzerland and Taiwan.

The number of patients in each individual study ranged from 85 to 334 913. The mean age ranged from 41 to 82.5 years. Percentage of women included in each study ranged from 8.4% to 34.7%. In terms of patient comorbidities, the prevalence of diabetes was 2.6–59%, hypertension 7.2–78.6%, prior MI 2.3–68.7%, hyperlipidaemia 0–82.7%, smoking 0–71.1%, COPD 0–17.9%, angina 0–82.0%, previous cerebrovascular accident 0–21.2%, chronic renal failure 0–23.3% and prior PCI 0–23.9% (Supplementary Material, Table S3).

A detailed assessment of the quality of the individual studies is reported in Supplementary Material, Table S5. Detailed results of the meta-analysis are outlined in Figs 1 and 2, Supplementary Material, Figs S4–S13 and Tables 1 and 2.

Primary outcome

When compared to men, women were at higher risk for operative mortality (OR: 1.77, 95% CI: 1.64–1.92, P < 0.001) (Fig. 1). This finding was robust when comparing studies published prior and after the year 2000 (P-for-interaction = 0.31, Supplementary Material, Fig. S2) and when comparing unadjusted, regression-adjusted and propensity-matched studies (P-for-interaction = 0.56, Supplementary Material, Fig. S3).

Leave-one-out analysis confirmed solidity of the pooled estimates (Supplementary Material, Fig. S4) and funnel plot did not reveal any evidence of publication bias (Supplementary Material, Fig. S5).

Secondary outcomes

Female sex was associated with a higher risk for late mortality (IRR: 1.16, 95% CI: 1.06–1.26, P < 0.001) (Fig. 2). Similar to operative mortality, this finding remained true when comparing studies published prior to and after the year 2000 (P-for-interaction = 0.06, Supplementary Material, Fig. S6) and when comparing unadjusted, regression-adjusted and propensity-matched studies (P-for interaction = 0.66, Supplementary Material, Fig. S7). Females were also more likely than males to experience MACE (IRR: 1.40, 95% CI: 1.19–1.66, P < 0.001), MI (IRR: 1.28, 95% CI: 1.13–1.45, P < 0.001) and stroke (IRR: 1.31, 95% CI: 1.15–1.51, P > 0.001) (Supplementary Material, Figs S8–S10). Females were not a higher risk of late RR (IRR: 0.99, 95% CI: 0.76–1.29, P = 0.95) (Supplementary Material, Fig. S11).

Meta-regression

At meta-regression, the percentage of women (beta = -1.90, P < 0.001) and the mean age of included patients (beta = -0.04, P < 0.001) were inversely associated with operative mortality. The rate of preoperative MI (beta = 0.01, P = 0.04), smoking (beta = 0.008, P = 0.03), renal failure (beta = 0.02, P = 0.03) and number of grafts performed (beta = 0.40, P < 0.001) in the included studies were associated with operative mortality. There were no variables significantly associated with late mortality (Table 2).

COMMENT

In this meta-analysis of 84 studies and 903 346 patients undergoing CABG, we found that operative mortality was worse for females when compared with males. Additionally, females were at significantly higher risk for late mortality and other important late events including MACE, MI and stroke, but not RR. At meta-regression, female sex and age were inversely associated with operative mortality while preoperative MI, smoking status, renal failure and the number of grafts were associated with operative mortality. Importantly, neither off-pump CABG (OPCABG) usage nor use of MAG were associated with operative or late mortality. The results remained solid when comparing studies published prior and after the year 2000, as well as in studies using different techniques for risk adjustment.

In the only other meta-analysis investigating the impact of sex on outcomes following isolated-CABG, Alam *et al.* similarly found that females are a higher risk of short-, mid- and long-term mortality. Consistent with our analysis, the authors report increased operative and 30-day mortality rates in females (OR: 1.77, 95% CI: 1.67–1.88) as well as 1-year (OR: 1.31, 95% CI: 1.18–1.45) and 5-year (OR: 1.14, 95% CI: 1.08–1.20) mortality. These findings remained true in a subgroup analysis of propensity-matched

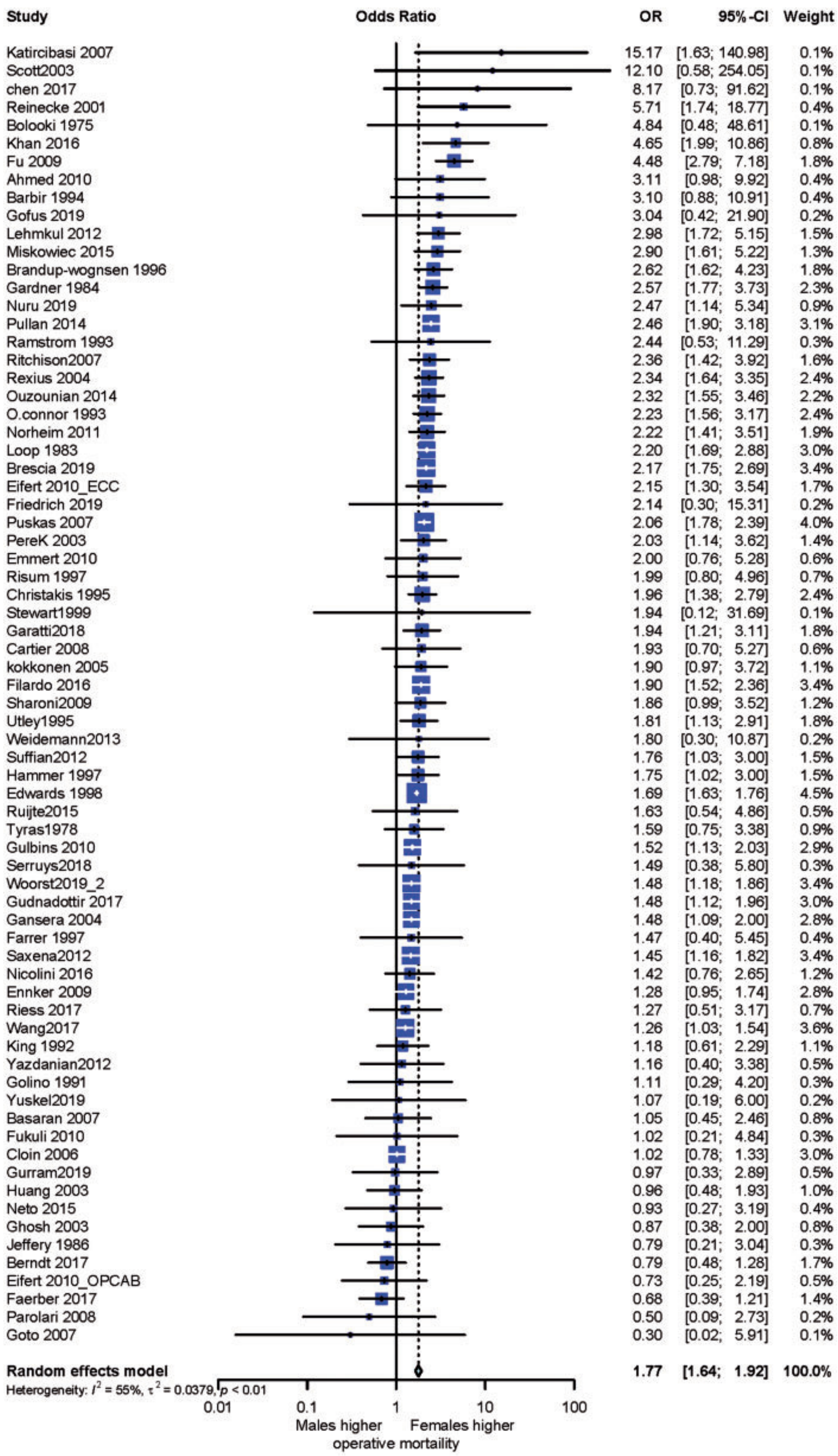


Figure 1: Forest plot for operative mortality. Forest plot showing the pooled rate of operative mortality following isolated coronary artery bypass grafting.

studies. Importantly, however, the authors did not report non-fatal events nor did they investigate the potential impact of operative technique or patients characteristics on outcomes [11].

Despite the improvement seen over the past decades [12], this analysis shows that females continue to remain at elevated risk for operative and late death as well as cardiac events including MACE, MI and stroke compared to males. It has been suggested that these differences in outcomes can be ascribed to different anatomic and biologic factors. Preoperatively, females undergoing CABG are older and typically have an increased prevalence of

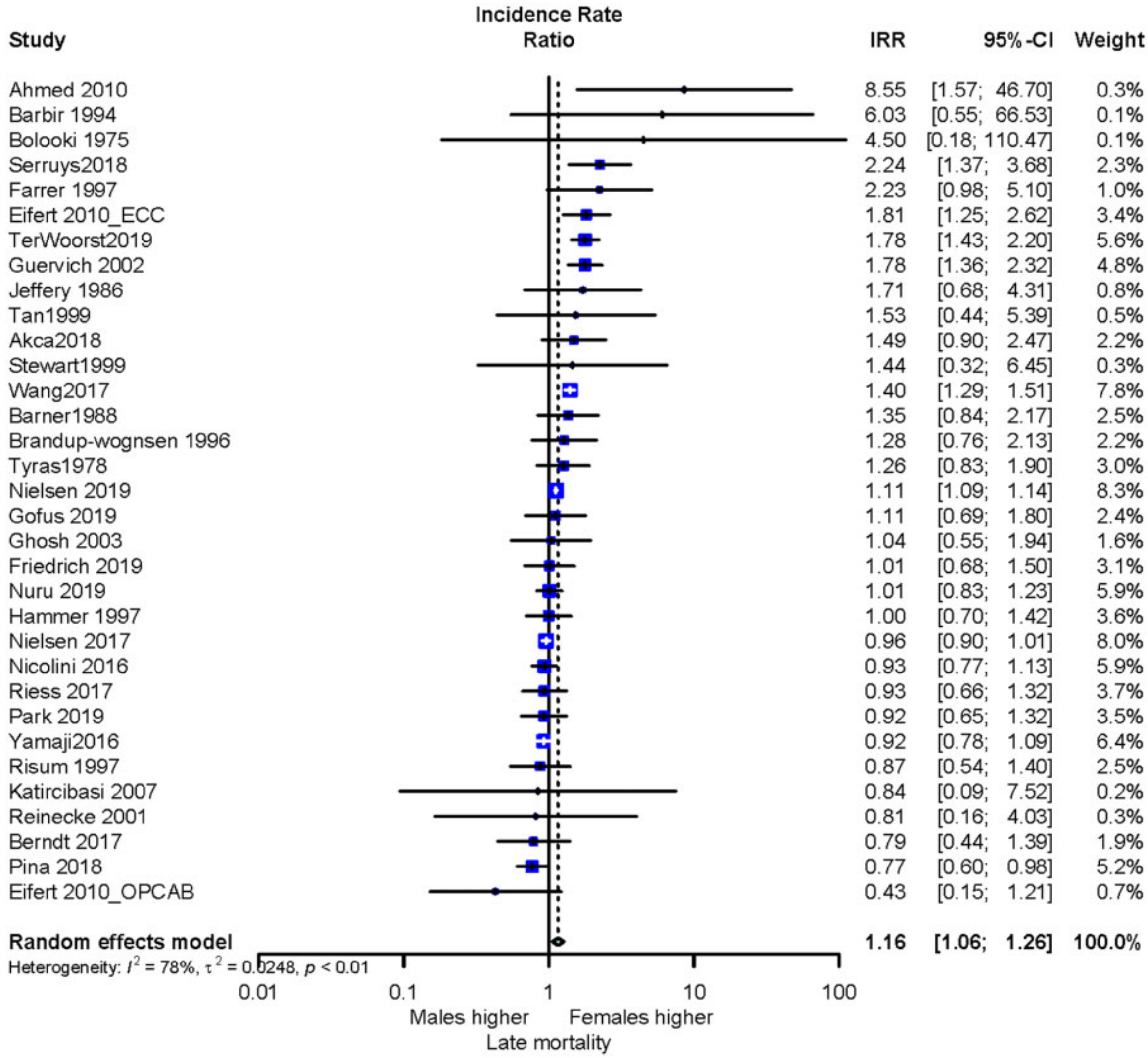


Figure 2: Forest plot for late mortality. Forest plot showing the pooled rate of late mortality following isolated coronary artery bypass grafting.

Table 1: Outcomes summary for included studies

	Studies	Patients	Effect estimate	Overall effect *P*-value	I^2	Heterogeneity *P*-value	*P*-interaction
Operative mortality	72	663 527	1.77 (1.64–1.92)	<0.001	0.56	<0.001	
After year 2000	54	280 782	1.73 (1.54–1.93)	<0.001	0.62	<0.001	0.31
Before year 2000	18	382 745	1.87 (1.69–2.06)	<0.001	0.11	0.33	0.31
Study type: regression-adjusted	52	563 900	1.75 (1.59–1.92)	<0.001	0.53	<0.001	0.56
Study type: unadjusted	9	7646	2.06 (1.54–2.75)	<0.001	0.02	0.41	0.56
Study type: PSM	11	91 981	1.82 (1.42–2.34)	<0.001	0.75	<0.001	0.56
Late mortality	33		1.16 (1.06–1.26)	<0.001	0.78	<0.001	
After year 2000	22		1.14 (1.03–1.26)	0.01	0.84	<0.001	0.60
Before year 2000	11		1.20 (1.01–1.44)	0.04	0	0.58	0.60
Study type: regression-adjusted	40		1.28 (1.14–1.44)	<0.001	0.47	<0.001	0.66
Study type: unadjusted	22		1.15 (1.03–1.28)	0.01	0.77	<0.001	0.66
Study type: PSM	8		1.35 (0.96–1.89)	0.08	0.57	0.02	0.66
Late MI	39		1.28 (1.13–1.45)	<0.001	0.48	<0.001	
Late stroke	45		1.31 (1.15–1.51)	<0.001	0.36	0.01	
Late RR	12		0.99 (0.76–1.29)	0.95	0.47	0.04	
Late MACE	8		1.4 (1.19–1.66)	<0.001	0.62	0.01	

MACE: major adverse cardiac events; MI: myocardial infarction; PSM: propensity score matched; RR: repeat revascularization.

Table 2: Association of key preoperative and intraoperative variables with operative and late mortality at meta-regression (significant results are in bold)

Variable	Operative mortality Beta ± SD, *P*-value	Late mortality Beta ± SD, *P*-value
Mean age	**−0.04 ± 0.009, *P* < 0.0001**	-0.02 ± 0.01, *P* = 0.14
Female	**−1.90 ± 0.54, *P* < 0.001**	-0.46 ± 0.66, *P* = 0.49
Diabetes	0.008 ± 0.005, *P* = 0.10	0.006 ± 0.007, *P* = 0.39
Hypertension	0.002 ± 0.004, *P* = 0.70	0.003 ± 0.005, *P* = 0.50
Prior MI	**0.01 ± 0.005, *P* = 0.04**	-0.006 ± 0.005, *P* = 0.21
Hyperlipidaemia	0.006 ± 0.004, *P* = 0.16	0.000 ± 0.01, *P* = 0.99
Smoking	**0.008 ± 0.004, *P* = 0.03**	0.01 ± 0.007, *P* = 0.08
COPD	-0.002 ± 0.01, *P* = 0.90	0.006 ± 0.03, *P* = 0.82
Angina	0.002 ± 0.003, *P* = 0.55	0.004 ± 0.005, *P* = 0.47
Stroke	0.018 ± 0.02, *P* = 0.38	-0.02 ± 0.02, *P* = 0.33
Renal failure	**0.02 ± 0.01, *P* = 0.03**	0.02 ± 0.01, *P* = 0.16
Prior PCI	-0.008 ± 0.01, *P* = 0.53	-0.04 ± 0.03, *P* = 0.14
No. of grafts	**0.40 ± 0.11, *P* < 0.001**	0.53 ± 0.36, *P* = 0.14
OPCABG	-0.003 ± 0.005, *P* = 0.61	-0.01 ± 0.006, *P* = 0.09
MAG	-0.001 ± 0.004, *P* = 0.90	-0.009 ± 0.02, *P* = 0.58

COPD: chronic obstructive pulmonary disease; CPB: cardiopulmonary bypass; ICU: intensive care unit; MAG: multiple arterial grafting; MI: myocardial infarction; OPCABG: off-pump coronary artery bypass grafting; PCI: percutaneous coronary intervention.

clinically important comorbidities such as diabetes mellitus, hypertension and peripheral vascular disease—all known risk factors for poor outcomes [13, 14]. In the majority of the pooled studies, females were older with higher prevalence of preoperative comorbidities. These baseline differences may explain why females were at a higher risk of poor outcomes, although our findings were solid for any level of statistical adjustment used. Importantly, these differences are not without consequence, as we identified preoperative MI, smoking status and renal failure as associated with operative mortality.

Notably, the operative technique had no impact on outcomes: OPCABG and MAG use were not associated with operative or late mortality. Additionally, our analysis did not find a significant difference in late RR between males and females. Prior studies have shown that females have smaller calibre coronary arteries, independent of body size, a known risk factor for graft failure [15, 16]. Some have proposed to increase the use of MAG to help compensate for these factors. The utility of MAG in females, however, remains a matter of debate. An analysis by Rocha *et al.* [17] showed significantly lower rates of arterial grafting in females, with improved outcomes when compared with single arterial grafting strategies. Alternatively, Kurlansky *et al.* [18] reported no difference in late survival at 12 years in a propensity-matched analysis of females undergoing MAG versus Single Arterial Grafting (SAG) . Of note, observational evidence suggests that MAG use may benefit younger patients in particular, and females typically present at an older age [19].

Similarly, the use of OPCABG to improve outcomes in females remains uncertain. An analysis by Puskas *et al.* [20] demonstrated a decrease in the rate of major adverse events for females undergoing OPCABG when compared to those undergoing on-pump CABG. Conversely, a report by Fu *et al.* [21] showed similar late survival, but an increase in the adjusted risk of major cardiac and cerebral events postoperatively following OPCABG. The authors posit that the smaller luminal diameter of coronary arteries in females may contribute to incomplete revascularization and perhaps explain an increase in late adverse events. While our analysis did not specifically investigate the impact of OPCABG on late MACE, the lack of a difference in both operative and late mortality is an important finding when considering the optimal operative strategy.

Finally, no difference in the primary outcome was observed when analysing studies using different types of risk adjustment. However, of the 13 propensity-matched analyses included, 5 showed higher rates of mortality for female undergoing isolated CABG [21–25], while the remaining 8 reported no difference [26–33]. Notably, these analyses also report conflicting results with respect to postoperative events including stroke and MI. When investigating sex-related differences, observational propensity-matching studies likely constitute the highest level of evidence and this apparent contradiction claim for further studies, potentially involving patient-level data, to confirm our findings.

Limitations

There are several limitations to this analysis. Observational studies are open to confounders and bias. There is also significant clinical and methodological heterogeneity among studies. Not all studies included in the analysis reported long-term outcomes, including mortality. Statistical heterogeneity was high for most comparisons. Finally, despite the use of the meta-analytic method, some of the outcomes reported in the secondary or subgroup analyses may be underpowered, and the results of the meta-regression should be interpreted at the study- and not patient-level.

CONCLUSION

To conclude, females undergoing isolated CABG are at higher risk for operative and late mortality when compared with males. Females are also at higher risk of non-fatal events including MACE, MI and stroke. Our data confirm that even in the current era, outcomes of females undergoing CABG remain suboptimal and claim for studies to elucidate the causes of this finding and improve women's outcome.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

Author contribution

N. Bryce Robinson: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. **Ajita Naik:** Data curation; Methodology; Validation; Writing—original draft; Writing—review & editing. **Mohamed Rahouma:** Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Visualization; Writing—original draft; Writing—review & editing. **Mahmoud Morsi:** Conceptualization; Data curation; Formal analysis; Visualization; Writing—original draft; Writing—review & editing. **Drew Wright:** Conceptualization; Data curation; Formal analysis; Methodology; Writing—original draft; Writing—review & editing. **Irbaz Hameed:** Conceptualization;

Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Visualization; Writing—original draft; Writing—review & editing. **Antonino Di Franco:** Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. **Leonard N. Girardi:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Writing—original draft; Writing—review & editing. **Mario Gaudino:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

Reviewer information

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