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META-ANALYSIS
Cardiac and Vascular Surgery

Sex differences in outcomes after coronary artery bypass grafting: a pooled analysis of individual patient data

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See page 29 for the editorial comment for this article 'Why do women do worse after coronary artery bypass grafting?', by S.A.E. Peters and J. Kluin, https://doi.org/10.1093/eurheartj/ehab617.

Aims Data suggest that women have worse outcomes than men after coronary artery bypass grafting (CABG), but results have been inconsistent across studies. Due to the large differences in baseline characteristics between sexes, suboptimal risk adjustment due to low-quality data may be the reason for the observed differences. To overcome this limitation, we undertook a systematic review and pooled analysis of high-quality individual patient data from large CABG trials to compare the adjusted outcomes of women and men.

Methods and results The primary outcome was a composite of all-cause mortality, myocardial infarction (MI), stroke, and repeat revascularization (major adverse cardiac and cerebrovascular events, MACCE). The secondary outcome was all-cause mortality. Multivariable mixed-effect Cox regression was used. Four trials involving 13 193 patients (10 479 males; 2714 females) were included. Over 5 years of follow-up, women had a significantly higher risk of MACCE [adjusted hazard ratio (HR) 1.12, 95% confidence interval (CI) 1.04–1.21; $P = 0.004$] but similar mortality (adjusted HR 1.03, 95% CI 0.94–1.14; $P = 0.51$) compared to men. Women had higher incidence of MI (adjusted HR 1.30, 95% CI 1.11–1.52) and repeat revascularization (adjusted HR 1.22, 95% CI 1.04–1.43) but not stroke (adjusted HR 1.17, 95% CI 0.90–1.52). The difference in MACCE between sexes was not significant in patients 75 years and older. The use of off-pump surgery and multiple arterial grafting did not modify the difference between sexes.

Conclusions Women have worse outcomes than men in the first 5 years after CABG. This difference is not significant in patients aged over 75 years and is not affected by the surgical technique.

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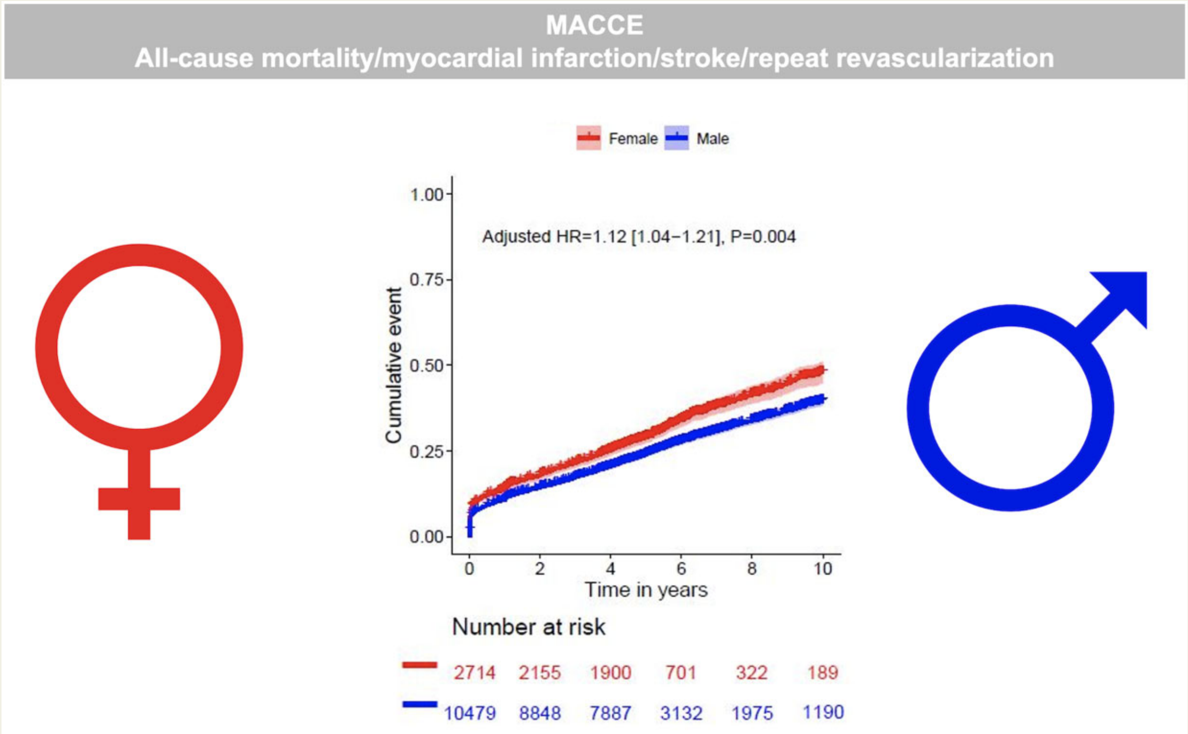
Graphical Abstract



Risk of major adverse cardiac and cerebrovascular events (all-cause mortality/myocardial infarction/stroke/repeat revascularization) in women vs. men undergoing coronary artery bypass surgery (curves represent unadjusted estimates). HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

Keywords CABG • Sex • Women

Introduction

Coronary artery bypass grafting (CABG) is the most commonly performed cardiac surgery procedure in adults.[1] In the USA, every year ∼200 000 patients undergo CABG and of them between 25% and 30% are women.[2]

Registries and chart review studies have reported worse early and late outcomes for women compared to men after CABG,[3,4] although this finding has not been consistent in all the published series.[5,6]

It is well known that there are key differences in baseline clinical characteristics and in the type and extent of coronary artery disease between men and women referred for CABG.[5,7] A critical part of any comparison of the CABG outcomes of men and women is the adjustment for this high baseline heterogeneity. Clinical charts and registries have important limitations in terms of granularity and quality of the data, and adjusted estimates based on those datasets have high risk of residual bias and unmeasured confounders. Randomized controlled trials (RCTs) minimize heterogeneity by including only a selected subgroup of the general population and have higher data quality. It is likely that the effectiveness of statistical adjustment and the chances of detecting true sex-related differences are maximized when using RCT-derived data.

However, the proportion of women enrolled in RCTs in cardiovascular medicine is low[8] and individual trials are underpowered to explore sex-related differences in outcomes.

To overcome these limitations, we performed a systematic review and pooled analysis of the individual patient data from the largest CABG trials to compare postoperative and mid-term outcomes of men and women undergoing CABG surgery after adjusting for prognostically important baseline clinical and surgical characteristics.

Methods

Study protocol

The protocol for the primary and secondary analyses of this study was published a priori.[9] Ethics approval and participants' consent were obtained locally by each trial team. The Weill Cornell Medicine Institutional Review Board waived the need for ethics approval for the pooled analysis (protocol #: 20-0902272). The present article was written in accordance with the Individual Patient Data–Preferred Reporting Items for Systematic Reviews and Meta Analyses (IPD-PRISMA) recommendations.

Selection of the trials

A systematic literature search was performed to identify all CABG RCTs (i.e. RCTs where all patients underwent or were expected to undergo CABG). Ovid MEDLINE, Ovid Embase, and Cochrane Trials (Wiley) were searched. The following keywords were used, in combination with the Boolean operator 'or': 'CABG' and 'coronary artery bypass'. We decided to include only CABG trials and to exclude trials comparing CABG to other interventions to minimize the potential heterogeneity related to the inclusion of patients who were acceptable candidates for both surgical and non-surgical interventions. To minimize the small-study effect,[10] trials were considered for inclusion only if they had a sample size ≥400 patients. Additional inclusion criteria were that trials: (i) enrolled both men and women, (ii) had a follow-up ≥5 years, and (iii) were written in English. The full search strategy is provided in the Supplementary material online, *Appendix*.

Two independent investigators performed the eligibility assessment (A.D.F. and M.G.); disagreements were discussed and resolved by consensus. The reference lists of the selected articles were also searched for relevant publications. For overlapping studies, the largest series or the series with the longest follow-up were considered.

Data collection and merging

After identification of eligible trials, the individual trials' teams were contacted and all agreed to data sharing. Detailed specifications of core minimum de-identified data requirements were provided to each trial team. De-identified data were received by the coordinating centre at Weill Cornell Medicine and checked for quality, completion, and consistency with previous publications. Data were checked for missing values, intra-field data integrity, and inter-field inconsistencies both within each RCT and across the RCTs. Discrepancies were resolved through direct consultation with the individual trials' teams. Data elements were then consolidated into a final database. The list of the variables collected in each trial is provided in Supplementary material online, *Table S1*.

Outcomes

The primary outcome was a composite of all-cause mortality, any myocardial infarction (MI), any stroke, and any repeat revascularization (major adverse cardiac and cerebrovascular events, MACCE). The secondary outcome was all-cause mortality. The tertiary outcomes were a composite of death and stroke and operative mortality, defined as death in hospital or within 30 days after surgery. Each individual non-fatal component of the composite outcome was also evaluated separately. For all events, individual trial definitions were used (details are in Supplementary material online, *Table S2*). All endpoints were compared by sex groups.

Statistical analysis

Baseline and intraoperative characteristics in the two groups were reported as numbers and percentages for categorical variables. For continuous variables normality was assessed using the Shapiro–Wilk test and data reported as means and standard deviations or median and interquartile range as appropriate. Parametric or non-parametric tests were used to compare the two groups, based on normality. Outcomes were reported as frequencies and cumulative incidence. For non-fatal events the cumulative incidence was determined with all-cause mortality as a competing risk using Fine and Gray[11] proportional sub-hazards model.

Primary analysis

In the primary analysis, association between treatment and outcomes was estimated using a multivariable mixed-effect Cox regression model, with individual trials as a random effect, and baseline risk factors and surgical techniques as fixed terms. Fixed terms included in the multivariable models were all baseline and operative variables consistently reported across trials, which included: sex, age, diabetes, previous MI, left ventricular ejection fraction (LVEF) <50%, renal insufficiency (serum creatinine >200 µmol/L), body mass index (BMI), New York Heart Association (NYHA) Class III–IV, peripheral vascular disease (PVD), previous stroke, previous percutaneous coronary intervention (PCI), off- or on-pump surgery, number of arterial grafts used (no arterial grafts, SAG: single arterial graft, and MAG: multiple arterial grafts), and total number of grafts. The proportional hazards assumption was verified using Schoenfeld residuals. Missing preoperative data were all <0.1% of the total and were imputed with median or mode values for continuous and categorical variables, respectively (Supplementary material online, *Figure S1*).

Treatment effects were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Subgroup analysis and interaction terms were used to investigate the following potential sex effect modifiers in the primary analysis: age, diabetes, previous MI, LVEF, number of grafts, and surgical techniques (off- vs. on-pump and MAG vs. SAG). Non-linearity for the interaction between age and sex was assessed using spline analysis and model $\chi 2$ comparison. The cut-off point for age was identified as the intercept between two curves obtained by contrasting adjusted relative risk in the two groups against age.

The effect of sex on the primary endpoint was also calculated using a two-stage approach pooling β coefficients and relative standard error obtained from individual study multivariable Cox regression models. Meta-analytic estimates were obtained using a generic inverse variance method with a random effects model. Trial-level and pooled estimates were reported as HRs and 95% CIs. Heterogeneity across trials was assessed using I^2 statistics. I^2 values <25% defined low heterogeneity, 25–50% moderate heterogeneity, and >50% high heterogeneity. Leave-one-out analysis was used to assess the influence of individual trials on the pooled estimate.

Two explanatory analyses not described in the original analysis plan[9] were added *post hoc*:

(1) A landmark analysis starting at 30 days after randomization for the primary outcome. This analysis was adjusted using the same method described for the primary analysis.
(2) Age was explored as a modifier of the sex effect for the secondary outcome of all-cause mortality.

Secondary analysis

In the secondary analysis, we investigated the effects of two important CABG surgical techniques (off- vs. on-pump and MAG vs. SAG) on the primary outcome by sex. To account for non-randomized treatment allocation, propensity scores (PS) for each of the two techniques were developed in women and men separately using a gradient boosting machine logistic regression model. Variables included in the PS were age, diabetes, previous MI, LVEF <50%, renal insufficiency, BMI, NYHA Class III–IV, PVD, previous stroke, previous PCI, number of grafts, number of arterial grafts (for the off- vs. on-pump comparison only), and off-pump surgery (for the MAG vs. SAG comparison only). The individual trial identifier was included in the PS model to ensure a balance between subjects from each trial. The treatment effect was evaluated using inverse probability of treatment weighting with 'average effect of the treatment on treated'. Standardized mean differences were used to assess the balance of covariates between the two treatment groups. A value higher than 0.10 was considered as an indication of residual imbalance.

Supplementary analysis with focus on preoperative left ventricular ejection fraction

To better evaluate the effect of preoperative LVEF on the outcomes by sex, individual patient data from the STICHES (Surgical Treatment of Ischaemic Heart Failure Extension Study) trial[12] (comparing CABG with medical therapy in patients with LVEF ≤35% at 10-year follow-up—see Supplementary material online, *Appendix* for details of the trial) were obtained through the Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung and Blood Institute and added to the database used for the primary analysis. The statistical methods used for this supplementary analysis were the same used in the primary analysis; the only difference was the categorization of preoperative LVEF that in this analysis was performed using a three-, rather than two-, level classification (>50%, 30–50%, and <30%).

Supplementary analysis based on the Open Heart Surgery Registry

To evaluate potential differences in sex effect in a real-world population, we accessed the Open Heart Surgery Registry, the mandatory database of the state of New Jersey, to identify patients who underwent CABG in years 2000–2017. This database is maintained by the New Jersey Department of Health; data are collected by clinical staff at all hospitals performing cardiac surgery in the State. External medical audits verify data quality annually. Long-term clinical outcomes were obtained for individual patients by linking this Open Heart Surgery Registry with the New Jersey Cardiac Catheterization Registry, the New Jersey Discharge Data Collection System, and the New Jersey Vital Statistics death registry, as previously described.[13,14] Patients were followed up until 31 December 2019. The statistical methods used for this supplementary analysis were the same used in the primary analysis.

Supplementary analysis including trial-level data of percutaneous intervention vs. coronary artery bypass grafting

A trial-level meta-analysis was performed pooling aggregate data from the primary analysis and from the CABG arm of the largest trials comparing percutaneous interventions (PCI) and CABG. Details for this analysis are provided in the Supplementary material online, *Appendix*.

A fixed-order sequential testing method using an alpha level of 0.05 was used to adjust for multiple comparisons in the primary analysis. Significance testing was not performed for the secondary analysis nor for the non-fatal components of the primary composite outcome. For these analyses, only estimates of the association between treatment and outcomes and corresponding 95% CIs were provided, and the results were interpreted as exploratory. All *P*-values were two-sided. In all the analyses, the male group was used as the reference.

Statistical analyses were performed with R version 3.6.1. and the following packages: coxme, meta, prodlim, twang, Publish.

Results

A total of 1828 studies were identified from the literature search, of which 1225 were screened for eligibility. Four trials met the inclusion criteria [the Arterial Revascularization Trial (ART) the CABG Off or On Pump Revascularization Study (CORONARY), the German Off-

Table 1 Baseline and operative characteristics of the patients in the pooled sample

	Overall (n = 13 193)	Males (n = 10 479)	Females (n = 2714)	*P*-value
Age (years), mean (SD)	67.6 (9.5)	67.0 (9.5)	69.96 (9.4)	<0.001
Renal insufficiency, *n* (%)	270 (2.0)	215 (2.1)	55 (2.0)	0.99
Diabetes, *n* (%)	4418 (33.5)	3391 (32.4)	1027 (37.8)	<0.001
Previous MI, *n* (%)	5033 (38.1)	4070 (38.8)	963 (35.5)	0.001
LVEF <50%, *n* (%)	7196 (54.5)	5860 (55.9)	1336 (49.2)	<0.001
BMI (kg/m^2), mean (SD)	27.9 (4.7)	27.77 (4.5)	28.51 (5.2)	<0.001
NYHA Class III–IV, *n* (%)	3700 (28.0)	2758 (26.3)	942 (34.7)	<0.001
Hypertension, *n* (%)	8159 (61.8)	6528 (62.3)	1631 (60.1)	<0.001
Hyperlipidaemia, *n* (%)	8722 (66.1)	7169 (68.4)	1553 (57.2)	0.10
COPD, *n* (%)	796 (6.0)	627 (5.9)	169 (6.2)	0.92
PVD, *n* (%)	1710 (13.0)	1320 (12.6)	390 (14.4)	0.016
Previous stroke, *n* (%)	1160 (8.8)	880 (8.4)	280 (10.3)	0.002
Previous PCI, *n* (%)	2239 (17.0)	1766 (16.9)	473 (17.4)	0.50
Off-pump, *n* (%)	5324 (40.4)	4213 (40.2)	1111 (40.9)	0.50
Number of grafts, mean (SD)	3.1 (0.9)	3.2 (0.9)	2.9 (0.9)	<0.001
Number of arterial grafts, *n* (%)				<0.001
0	598 (4.5)	423 (4.0)	175 (6.4)	
1	9068 (68.7)	7119 (67.9)	1949 (71.8)	
≥2	3527 (26.7)	2937 (28.0)	590 (21.7)	

BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SD, standard deviation.

Table 2 Operative outcomes in the pooled sample

	Overall (n = 13 193), n (%)	Males (n = 10 479), n (%)	Females (n = 2714), n (%)	Adjusted OR[a] (95% CI)
MACCE	1075 (8.1)	807 (7.7)	268 (9.9)	1.28 (1.10–1.49)
Mortality[b]	243 (1.8)	181 (1.7)	62 (2.3)	1.27 (0.94–1.72)
MI	714 (5.4)	542 (5.2)	172 (6.3)	1.27 (1.06–1.53)
Stroke	174 (1.3)	125 (1.2)	49 (1.8)	1.34 (0.95–1.90)
Repeat revascularization	61 (0.5)	44 (0.4)	17 (0.6)	1.29 (0.72–2.33)
Reoperation for bleeding	394 (3.0)	321 (3.1)	73 (2.7)	0.84 (0.65–1.10)
Renal replacement therapy	378 (2.9)	293 (2.8)	85 (3.1)	1.18 (0.89–1.57)
Postoperative atrial fibrillation	2350 (17.8)	1937 (18.5)	413 (15.2)	0.82 (0.73–0.94)
Mediastinitis	89 (0.7)	70 (0.7)	19 (0.7)	0.98 (0.58–1.66)

BMI, body mass index; CI, confidence interval; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NYHA, New York Heart Association; OR, odds ratio; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.
[a]Adjusted using a multivariable regression model with individual trials as a random effect including age, diabetes, previous MI, LVEF <50%, renal insufficiency (serum creatinine >200 µmol/L), BMI, NYHA Class III–IV, PVD, previous stroke, previous PCI, off-pump surgery, number of arterial grafts used (no arterial grafts, single arterial grafts, and multiple arterial grafts), and total number of grafts.
[b]Unadjusted OR (95% CI): 1.25 (0.93–1.69).

Table 3 Results of the analysis for the primary and secondary outcomes and the non-fatal individual components of the primary outcome

	Overall (n = 13 193)	Males (n = 10 479)	Females (n = 2714)	Unadjusted HR (95% CI)	P-value (unadjusted comparison)	Adjusted HR[a] (95% CI)	P-value (adjusted comparison)
Follow-up (years), mean (SD)	5.7 (2.5)	5.8 (2.5)	5.3 (2.4)	—	—	—	—
MACCE, n (%)	3924 (29.7)	3012 (28.7)	912 (33.6)	1.19 (1.11–1.29)	<0.001	1.12 (1.04–1.21)	0.004
All-cause mortality, n (%)	2375 (18.0)	1817 (17.3)	558 (20.6)	1.11 (1.00–1.22)	0.04	1.03 (0.94–1.14)	0.51
All-cause mortality/stroke, n (%)	607 (22.4)	1987 (19.0)	2594 (19.7)	1.11 (1.01–1.22)	0.03	1.04 (0.95–1.14)	—
MI, n (%)	924 (7.0)	703 (6.7)	221 (8.1)	1.33 (1.14–1.55)	—	1.30 (1.11–1.52)	—
Stroke, n (%)	350 (2.7)	270 (2.6)	80 (2.9)	1.26 (0.98–1.62)	—	1.17 (0.90–1.52)	—
Repeat revascularization, n (%)	940 (7.1)	732 (7.0)	208 (7.7)	1.25 (1.07–1.46)	—	1.22 (1.04–1.43)	—

BMI, body mass index; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.
[a]Adjusted for age, diabetes, previous MI, LVEF <50%, renal insufficiency (serum creatinine >200 µmol/L), BMI, NYHA Class III–IV, PVD, previous stroke, previous PCI, off-pump surgery, number of arterial grafts used (no arterial grafts, single arterial grafts, and multiple arterial grafts), and total number of grafts.

Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE), and the Project of Ex-Vivo Vein Graft Engineering via Transfection IV trial (PREVENT IV)].[15–18] The principal investigators of all the trials were contacted and all agreed to share the data (the IPD-PRISMA flowchart is provided in Supplementary material online, *Figure S2*).

Trials description

In the ART trial,[15] 3102 CABG patients were randomly assigned to bilateral or single internal thoracic artery grafting (1548 vs. 1554 patients, respectively). Patients were enrolled from 2004 to 2007 at 28 hospitals from 4 continents and a total of 7 countries. At 10-year follow-up, the authors found no significant between-group difference in the rate of death from any cause (HR 0.96, 95% CI 0.82–1.12) and in the composite outcome of death, MI, or stroke (HR 0.90, 95% CI 0.79–1.03).

In the CORONARY trial,[16] 4752 patients were randomly assigned to undergo off-pump or on-pump CABG (2375 vs. 2377 patients, respectively). Patients were enrolled from 2006 to 2011 at 79 centres from 4 continents and 19 countries. At 4.8-year follow-up, the rate of the composite outcome of death, stroke, MI, renal failure, or repeat revascularization was similar between groups (HR 0.98, 95% CI 0.87–1.10).

In the GOPCABE trial,[17] 2539 patients aged ≥75 years were randomly assigned to undergo off-pump or on-pump CABG (1271 vs. 1268 patients, respectively). Patients were enrolled from 2008 to

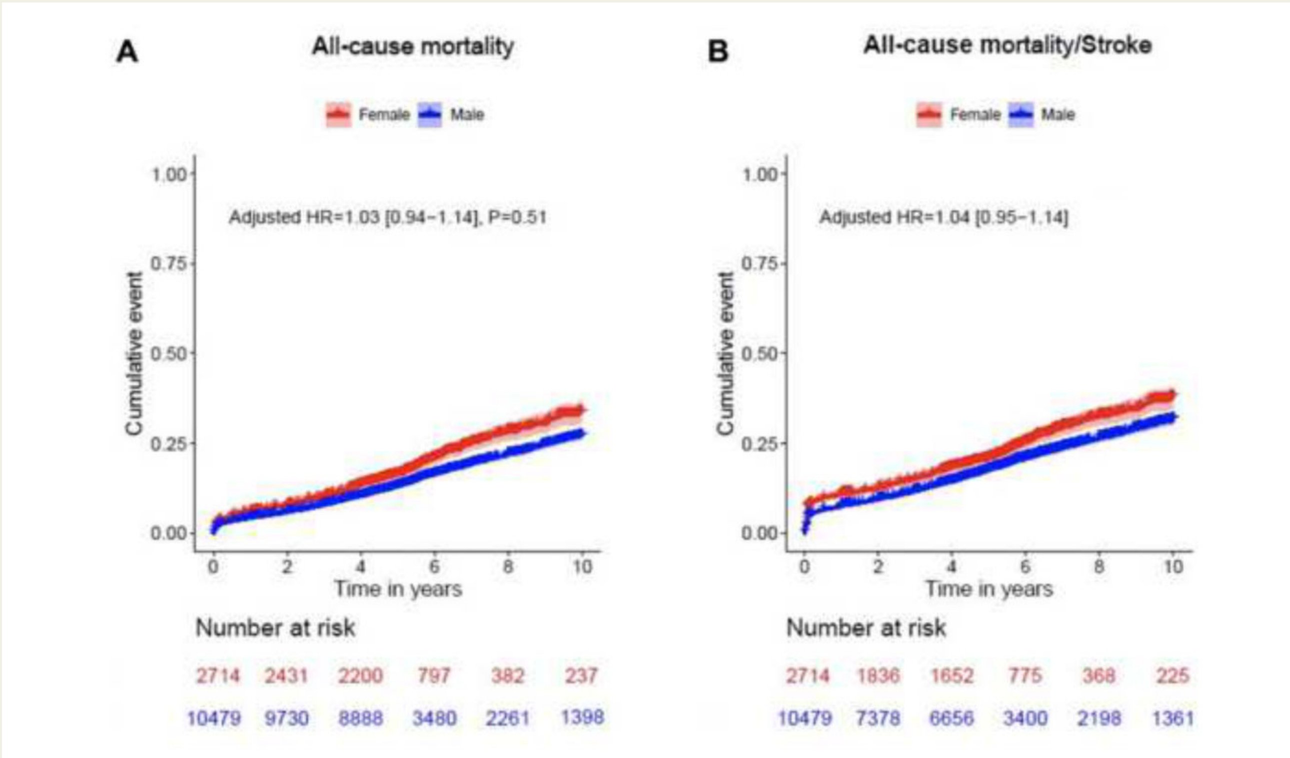


Figure 1 Risk of (*A*) all-cause mortality and (*B*) all-cause mortality/stroke in women vs. men undergoing coronary artery bypass surgery (curves represent unadjusted estimates). HR, hazard ratio.

2011 at 12 centres in Germany. At 5-year follow-up, survival rates (HR 1.03, 95% CI 0.89–1.19) and the combined outcome of death, MI, and repeat revascularization (HR 1.03, 95% CI 0.89–1.18) were similar in the two groups.

In the PREVENT IV trial,[18] 3014 patients undergoing primary CABG surgery with at least two planned saphenous vein grafts were randomly assigned to undergo *ex vivo* vein graft treatment with either edifoligide or placebo (1508 vs. 1506 patients, respectively). Patients were enrolled from 2002 to 2003 at 107 sites in the USA. At 5-year follow-up, the rates of the adjusted composite outcome of death, MI, or revascularization (HR 1.15, 95% CI 1.00–1.31) and of death or MI (HR 1.21, 95% CI 1.03–1.43) were significantly higher in patients receiving saphenous vein grafts with multiple vs. single distal targets.

Baseline patients' characteristics and operative outcomes in the individual trials are provided in Supplementary material online, *Tables S3 and S4*, respectively.

Overall, 13 193 patients (10 479 men and 2714 women) were included. Baseline and operative characteristics from the pooled sample are summarized in *Table 1*. The female cohort was older and more symptomatic and had higher prevalence of comorbidities (diabetes, hypertension, PVD, previous stroke) compared to the male cohort. Intraoperatively, the rate of off-pump procedures was similar between women and men; women received a significantly lower number of grafts and arterial grafts.

The mean follow-up time was 5.3 ± 2.4 and 5.8 ± 2.5 years in the female and male cohorts, respectively.

Primary analysis

Operative results are summarized in *Table 2*; operative mortality was similar for women and men [2.3% vs. 1.7%, adjusted odds ratio (OR) 1.27, 95% CI 0.94–1.72]. Women had a higher incidence of perioperative MI (6.3% vs. 5.2%, adjusted OR 1.27, 95% CI 1.06–1.53), a lower incidence of atrial fibrillation (15.2% vs. 18.5%, adjusted OR 0.82, 95% CI 0.73–0.94), and similar rates of stroke, repeat revascularization, reoperation for bleeding, need for renal replacement therapy, and mediastinitis compared to men.

Over 5 years of follow-up, women had a significantly higher risk of MACCE compared to men (adjusted HR 1.12, 95% CI 1.04–1.21, $P = 0.004$) (*Table 3* and *Graphical abstract*) but similar risk of all-cause mortality (adjusted HR 1.03, 95% CI 0.94–1.14, $P = 0.51$) (*Figure 1A*) and composite of all-cause mortality and stroke (adjusted HR 1.04, 95% CI 0.95–1.14) (*Figure 1B*).

When analysing the non-fatal individual components of the composite outcome, women had higher incidence of MI (adjusted HR 1.30, 95% CI 1.11–1.52) and repeat revascularization (adjusted HR 1.22, 95% CI 1.04–1.43), but not of stroke (adjusted HR 1.17, 95% CI 0.90–1.52) (*Table 3* and *Figure 2*).

Results of the analysis on sex effect modifiers are provided in *Figure 3*. Age had a significant interaction (spline 3 knots) with sex on the long-term risk of MACCE (*Figure 4*). Age 75 was the cut-off for equipoise between women and men (adjusted HR 1.29, 95% CI 1.17–1.43 for age <75 years vs. adjusted HR 0.94, 95% CI 0.83–1.05 for age ≥75; interaction $P < 0.001$). Off- vs. on-pump surgery (interaction $P = 0.22$),

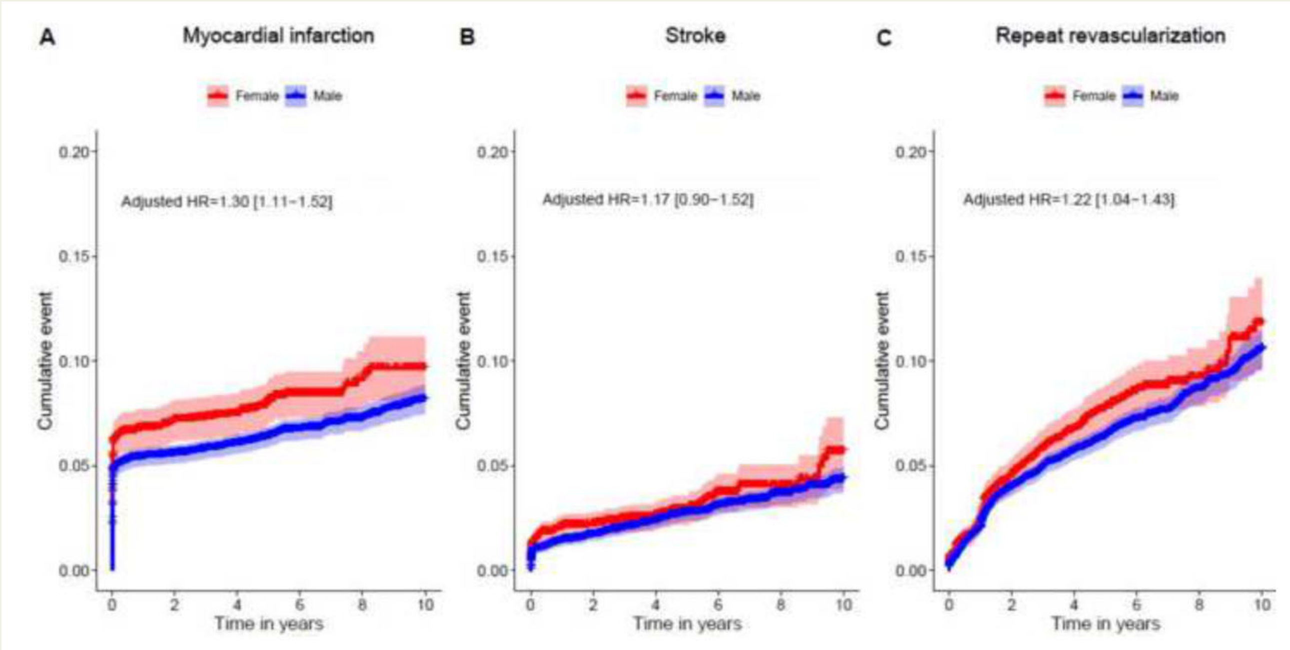


Figure 2 Risk of (*A*) myocardial infarction, (*B*) stroke, and (*C*) repeat revascularization in women vs. men undergoing coronary artery bypass surgery (curves represent unadjusted estimates). HR, hazard ratio.

use of MAG vs. SAG (interaction $P = 0.39$), diabetes (interaction $P = 0.09$), prior MI (interaction $P = 0.26$), and LVEF <50% (interaction $P = 0.07$) did not modify the effect of sex on MACCE.

Age had a similar modifier effect on all-cause mortality with the same 75 years cut-off (adjusted HR 1.18, 95% CI 1.02–1.36 for age <75; adjusted HR 0.90, 95% CI 0.79–1.03 for age ≥75; interaction $P < 0.001$) (Supplementary material online, *Figure S3*).

In the landmark analysis starting at 30 days from randomization, female sex was not associated with an increased risk of MACCE (adjusted HR 1.06, 95% CI 0.97–1.16) (*Figure 5*).

The pooled estimate for the primary endpoint from the two-stage analysis was consistent with the main analysis (Supplementary material online, *Figures S4 and S5*).

Secondary analysis

Propensity scores-weighting achieved good balance between off- vs. on-pump and MAG vs. SAG groups for both sexes (Supplementary material online, *Tables S5–S8*). The risk of MACCE was similar after off- vs. on-pump surgery for women (adjusted HR 0.94, 95% CI 0.81–1.08) and men (adjusted HR 1.02, 95% CI 0.94–1.10) (Supplementary material online, *Figure S6A and B*). When compared to SAG, MAG was associated with a reduction in the risk of MACCE in men (adjusted HR 0.86, 95% CI 0.78–0.95) but not in women (adjusted HR 0.97, 95% CI 0.80–1.17) (Supplementary material online, *Figure S6C and D*).

Supplementary analyses

The results of the analysis including the STICHES trial were consistent with the primary analysis (adjusted HR for MACCE 1.12, 95% CI 1.04–1.21; adjusted HR for mortality 1.03, 95% CI 0.94–1.14) (Supplementary material online, *Table S9* and *Figure S7*). Preoperative LVEF was a significant sex effect modifier; women with preoperative LVEF <30% had lower risk of MACCE compared to men, while the opposite was seen among patients with LVEF >30% (Supplementary material online, *Figure S8*).

The results of the analysis of the Open Heart Surgery Registry were consistent with the primary analysis (HR for MACCE 1.15, 95% CI 1.13–1.15, HR for mortality 1.04, 95% CI 1.004–1.07) (Supplementary material online, *Table S10* and *Figure S9*).

In the trial-level meta-analysis including the PCI vs. CABG trials, women had higher risk of MACCE and mortality than men (HR 1.09, 95% CI 0.85–1.39 and HR 1.41, 95% CI 1.04–1.92, respectively) (Supplementary material online, *Figure S10*).

Discussion

In this analysis of 13 193 patients (2714 women) followed for a mean of 5 years, we found that, after CABG, women have higher adjusted incidence of adverse cardiac and cerebrovascular events, but similar mortality compared to men. The higher incidence of MACCE is mostly driven by a higher rate of MI and repeat revascularization.

A new and important finding is that the difference between sexes is inversely associated with age and disappears at 75 years. Coronary artery disease in young women has distinct pathophysiological features and outcomes; e.g. women more often have coronary dissection, microvascular dysfunction, spasm, or myocardial bridges than men and have higher mortality after acute coronary events.[7,19,20] In a large registry study including 51 187 patients (15 178 women),[21]

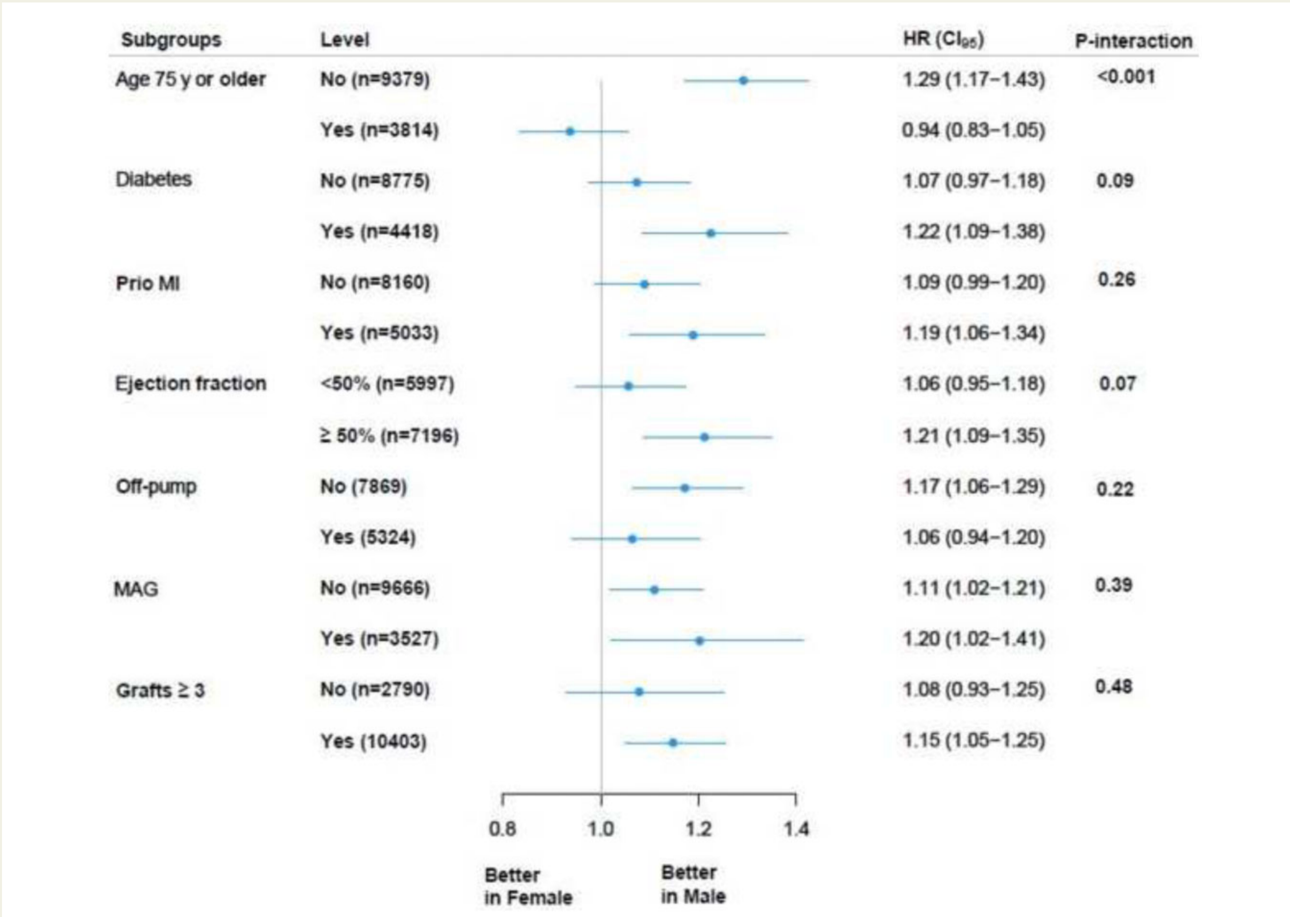


Figure 3 Sex effect modifiers in the primary analysis. CI, confidence interval; HR, hazard ratio; MAG, multiple arterial grafts; MI, myocardial infarction.

Vaccarino *et al.* found that women younger than 50 years had two times higher adjusted operative mortality after CABG compared to men of the same age range and that the difference in operative outcomes between sexes decreased with increasing age. It is possible that CABG is less effective in a younger female population, but this has not been investigated in details.

Another important finding is that preoperative LVEF was a significant sex effect modifier; while women with preoperative LVEF >30% had increased risk of MACCE compared to men, the opposite was true among patients with LVEF <30%.

We have also found that women have a higher risk of perioperative MI after CABG and in the landmark analysis excluding the early postoperative period, the difference in outcome between groups was clearly attenuated. Native coronary arteries and bypass conduits in women are generally smaller,[22,23] and there is *in vitro* evidence that they may have a higher tendency to spasm compared to men.[24,25] It is possible that the CABG procedure is technically more complex in women and that graft failure due to technical reasons may have played a role in the observed differences. The higher rate of perioperative MI may have also affected the mid-term outcomes.[26] The tendency to spasm[7,19] and the technical complexity are likely increased in younger women and this may explain the reported association of age with the difference in outcomes between sexes. These findings are hypothesis generating and require further investigation.

In the only published study-level meta-analysis investigating the impact of sex on outcomes following CABG, Alam *et al.*[27] pooled data from 20 studies and 966 492 patients (277 783 women) and found that female sex was associated with higher adjusted risk of operative mortality and that the mortality differences between sexes persisted at 5-year follow-up (OR 1.77, 95% CI 1.67–1.88 and OR 1.14, 95% CI 1.08–1.20, respectively).

Our analysis also suggests that variations in CABG surgical technique (off- vs. on-pump surgery and use of MAG vs. SAG) do not improve the outcomes of women and do not reduce the difference between sexes. This finding highlights the need to explore new modifications of the surgical technique or of postoperative protocols to improve CABG outcomes in women.

The secondary analyses comparing the effect of different surgical techniques in the two sexes suffer from inevitable treatment allocation and expertise biases[28] and were designed to provide exploratory data on the relative difference in treatment effect by sex, not on the absolute efficacy of the four techniques analysed.

Off-pump CABG was not associated with significant changes in outcomes both in men and women. This is concordant with the

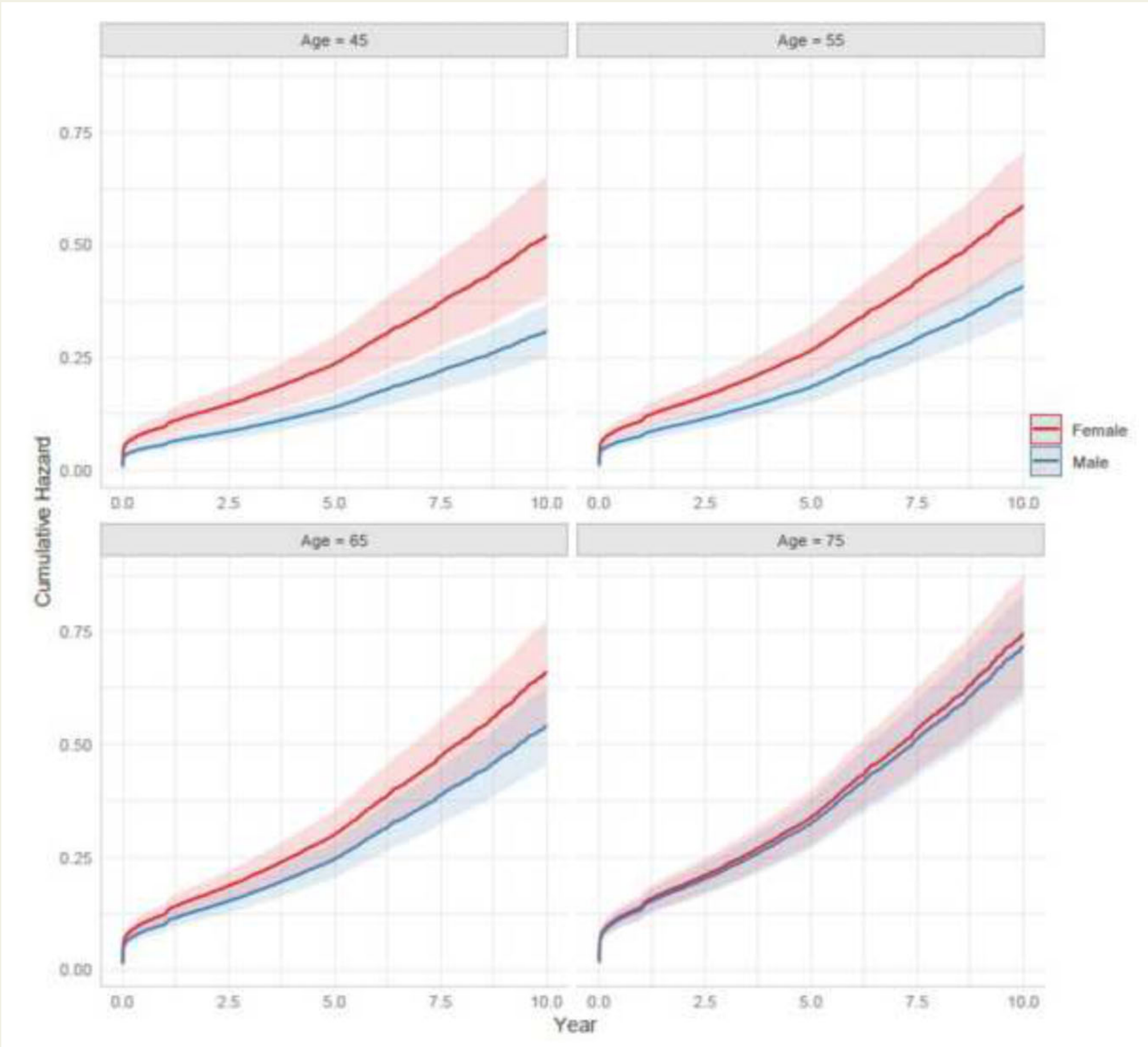


Figure 4 Association of sex across age groups with major adverse cardiac and cerebrovascular events (all-cause mortality/myocardial infarction/stroke/repeat revascularization).

results of RCTs and observational studies limited to surgeons with experience in the off-pump technique.[16,29] In contrast, MAG was associated with better outcomes in men, but not in women. The available observational evidence on the use of MAG in women is conflicting, with some studies suggesting and others refuting a clinical benefit for women who receive more than one arterial graft for CABG.[30–34] Data suggest that the potential benefit of MAG may be lost in higher risk patients,[13,35] and this may explain why women, who have worse baseline risk profile, may not benefit as much as men from MAG. Overall, our analysis suggests that a sex-related difference in the effect of MAG may exist and underlines the need for new and better evidence on this topic.

Several limitations of this study must be acknowledged. Outcome definitions and event adjudication were not standardized in the included trials, although all used an independent adjudication committee. It is likely that there was substantial heterogeneity in surgical techniques and postoperative protocols between the included trials and the individual participating sites. Finally, the cardiovascular event rate in CABG patients increases substantially after the fifth postoperative year and longer-term data are needed to confirm the present results (e.g. the benefit of MAG may become apparent in women with longer follow-up). On the other hand, results were solid in multiple sensitivity and supplementary analyses, even when including aggregate data from other trials and when repeating the analysis in a large real-world registry.

In conclusion, in a pooled analysis of four large CABG trials, we have found that, in the first 5 years after surgery, women have worse cardiac and cerebrovascular outcomes than men. The difference in

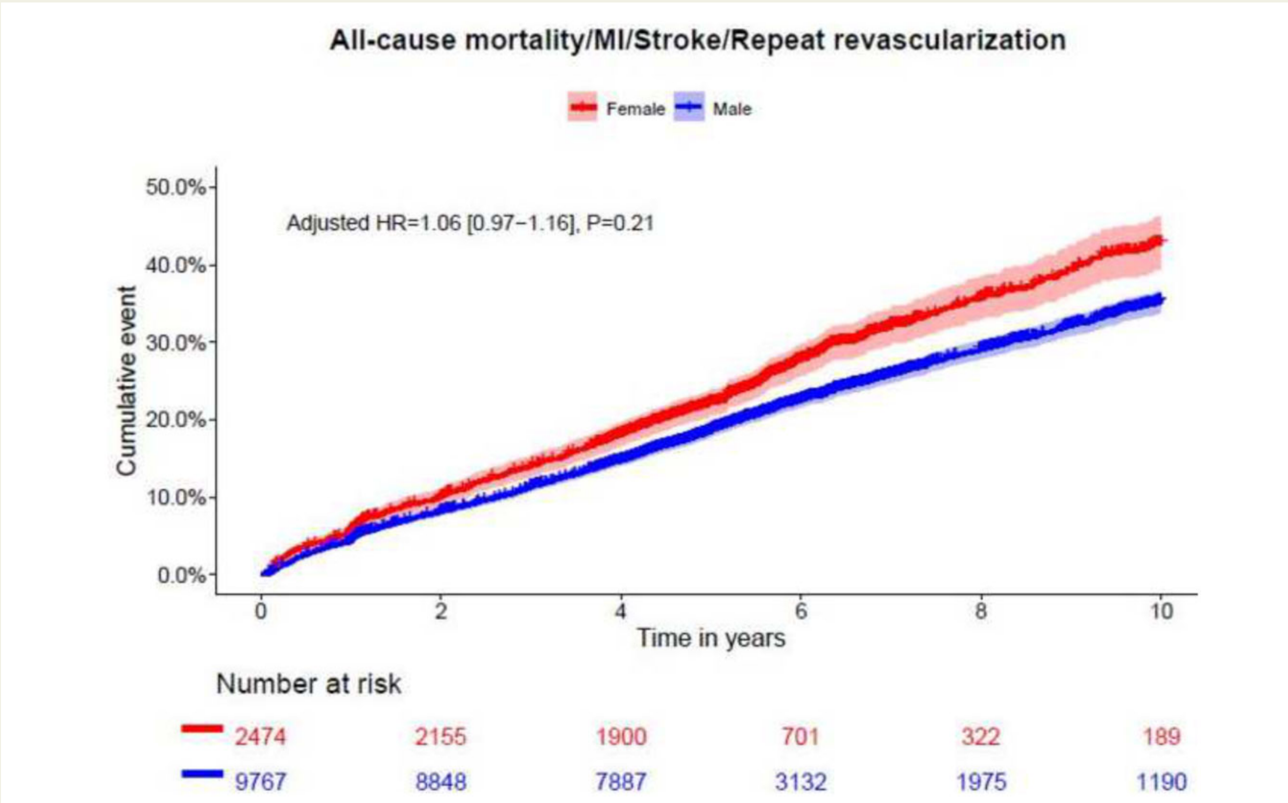


Figure 5 Landmark analysis for major adverse cardiac and cerebrovascular events (all-cause mortality/myocardial infarction/stroke/repeat revascularization) at 30 days (curves represent unadjusted estimates; time starts at 30 days after randomization). HR, hazard ratio; MI, myocardial infarction.

outcomes between the sexes is not evident after 75 years of age and is significantly affected by preoperative LVEF, but not by variations in the surgical technique used. Women have a higher risk of perioperative MI that may be due to technical factors and may be one of the reasons for the difference in mid-term outcomes.

Further effort in understanding and improving the outcome of women (and particularly younger women) undergoing CABG are needed.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: none declared.

Ethical approval

Ethics approval and participant consent was obtained locally by each trial team. The Weill Cornell Medicine Institutional Review Board waived the need for ethics approval for the pooled analysis (protocol #: 20-0902272).

Data availability

Data collected for the study will be made available by the corresponding author upon reasonable request after publication.

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