Original research

Multiple arterial coronary bypass grafting is associated with greater survival in women

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ABSTRACT

Objective Multiple arterial grafting (MAG) in coronary artery bypass grafting (CABG) is associated with higher survival and freedom from major adverse cardiac and cerebrovascular events (MACCEs) in observational studies of mostly men. It is not known whether MAG is beneficial in women. Our objectives were to compare the long-term clinical outcomes of MAG versus single arterial grafting (SAG) in women undergoing CABG for multivessel disease.

Methods Clinical and administrative databases for Ontario, Canada, were linked to obtain all women with angiographic evidence of left main, triple or double vessel disease undergoing isolated non-emergent primary CABG from 2008 to 2019. 1:1 propensity score matching was performed. Late mortality and MACCE (composite of stroke, myocardial infarction, repeat revascularisation and death) were compared between the matched groups with a stratified log-rank test and Cox proportional-hazards model.

Results 2961 and 7954 women underwent CABG with MAG and SAG, respectively, for multivessel disease. Prior to propensity-score matching, compared with SAG, those who underwent MAG were younger (66.0 vs 68.9 years) and had less comorbidities. After propensity-score matching, in 2446 well-matched pairs, there was no significant difference in 30-day mortality (1.6% vs 1.8%, p=0.43) between MAG and SAG. Over a median and maximum follow-up of 5.0 and 11.0 years, respectively, MAG was associated with greater survival (HR 0.85, 95% CI 0.75 to 0.98) and freedom from MACCE (HR 0.85, 95% CI 0.76 to 0.95).

Conclusions MAG was associated with greater survival and freedom from MACCE and should be considered for women with good life expectancy requiring CABG.

INTRODUCTION

Women remain under-represented in contemporary randomised clinical trials (RCTs) comparing revascularisation strategies. In trials comparing the use of radial arteries with saphenous vein grafting, 30% of enrolled patients were women.[1] In the Arterial Revascularization Trial comparing bilateral with single internal mammary artery (IMA) use, only 14% of enrolled patients were women.[2] Women are also under-represented in large observational studies comparing multiple arterial grafting with single arterial grafting (SAG) strategies for coronary artery bypass grafting (CABG). Rocha and colleagues compared three arteries to two arteries in over 11 000 patients and less than 15% of patients were women.[3] Given that women are under-represented in clinical trials that examine multiple arterial grafting strategies, whether women benefit from arterial grafting and the magnitude of treatment effect remain unknown. Furthermore, there are no RCTs that have shown the superiority of a multiple arterial grafting strategy over a SAG strategy, including the largest RCT to date, the ART trial which randomised 3102 patients to either a bilateral or single IMA grafting strategy and found no difference in survival or freedom from adverse cardiac events at 10 years.[2 4] As such, the objectives of this multicentre study were to determine whether multi-arterial grafting was associated with greater long-term survival and reduced major adverse cardiac and cerebrovascular events (MACCEs) compared with SAG in women in Ontario, Canada, over an 11-year period.

METHODS

Study overview

A retrospective propensity score-matched comparison of multiple arterial grafting (MAG) versus SAG in women from 1 October 2008 to 31 March 2019 was performed. Data from all 11 Ontario cardiac surgical centres were included through linkages of multiple clinical and administrative datasets housed at ICES (formerly known as the Institute for Clinical Evaluative Sciences) in Toronto, Ontario, Canada. ICES is Canada's largest health services research institute and holds multiple population-based health databases of the Ontario population. As a prescribed entity under Ontario's Personal Health Information Protection Act, ICES is able to collect, construct and store registries, link and analyse individual health data without the need to obtain individual patient consent (see link to Data and Privacy at www.ices.on.ca). The use of data in this project was authorised under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. The need for individual patient consent was waived. These datasets were linked using unique encoded identifiers and analysed at ICES. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. Similar to previously published studies, we included all women with angiographic evidence of multivessel coronary artery disease defined

as two-vessel including left anterior descending (LAD) with or without proximal LAD involvement, three-vessel disease, and patients with left main with or without additional vessel disease.[5 6] We included all isolated primary CABG cases with ≥2 bypasses and ≥1 arterial graft. We excluded those receiving concomitant cardiac procedures (ie, valve repair or replacement, aortic surgery), those undergoing cardiac reoperation and those in cardiogenic shock. Using a previously validated algorithm, physician billing claims were used to ascertain the total number of bypass grafts and arterial grafts used, including IMA or radial artery grafts.[3 7] Patients were grouped according to the number of arterial grafts. The MAG cohort and SAG cohort consisted of patients with ≥2 arterial grafts and one arterial graft, respectively.

Baseline characteristics

Baseline characteristics were obtained from the Canadian Institute of Health Information (CIHI) Discharge Abstract Database (DAD) using ICD-10 codes and the CorHealth Ontario Cardiac Registry using previously validated algorithms when available.[8] The Ontario Registered Persons Database was used to obtain sociodemographic information including postal code, which was linked to Statistics Canada's census data to obtain median neighbourhood income of individuals to serve as a proxy for socioeconomic status.

Outcomes

The primary outcome of this study was long-term survival, and all-cause mortality was ascertained from the RPDB. The secondary outcome of interest was MACCE, defined as the composite of death, any acute myocardial infarction, any stroke or repeat revascularisation, which were ascertained from the CIHI-DAD (Supplemental Appendix). CIHI-DAD was also used to ascertain tertiary outcomes including early death (defined as death within index hospitalisation or 30 days of procedure), in-hospital myocardial infarction, in-hospital stroke, incidence of sternal infection at 1 year and the long-term individual components of MACCE. The date of last-follow-up for all databases was 31 March 2019.

Statistical analysis

Baseline characteristics were compared between MAG and SAG in the overall sample using Student's t-test and χ^2 test for continuous and categorical variables, respectively. The rate of annual MAG utilisation was calculated for both men and women by dividing the number of subjects who underwent MAG by the total number of subjects in the MAG and SAG for that year. The annual rate of MAG utilisation was regressed by year and sex in a linear regression model to assess MAG utilisation trends over the course of the study period. Propensity score (PS) analysis was used to address potential confounding due to systematic differences in baseline characteristics between those undergoing MAG (exposure) and SAG (control). The PS for each patient was estimated using a multivariable logistic regression model on the exposure variable. We included 21 clinically relevant baseline characteristics and socioeconomic demographics (see supplemental material for full list). Subjects were matched on the logit of the PS using a 1:1 greedy nearest-neighbour with a calliper distance of 0.20 times the SD of the logit of the PS. The standardised mean difference (SMD) was calculated for each covariate to determine the quality of the match; a cut-off of 0.1 denoted acceptable balance. In PS-matched patients, the McNemar test, paired t-test and Wilcoxon signed-rank test were used to compare early binary outcomes, normally and non-normally distributed outcomes, respectively. In addition, we compared patients that were PS matched to those who were not matched. All tests were two sided and p values <0.05 were considered significant.

For long-term outcomes, a time to event analysis using Kaplan-Meier survival curves was conducted in PS-matched patients, using a stratified log-rank test to test the equality of the estimated survival curves for all-cause mortality and freedom from MACCE. The HR was estimated using a Cox proportional-hazards model, incorporating a robust sandwich-type variance estimate to account for the matched nature of the data.[9] For non-fatal outcomes of stroke, myocardial infarction (MI) and repeat revascularisation, the cumulative incidence function (CIF) was used to estimate the incidence of these events, accounting for death as a competing risk.[10] The cause-specific hazard models were used to regress the outcome on the treatment status variable, incorporating a robust variance estimator.

Sensitivity analysis

To address the potential for an institutional effect on outcomes and examine outcomes in the full sample, the PS was estimated using a hierarchical model that included institutional-specific random effects in addition to the baseline characteristics as described earlier. The PS scores were then applied in an inverse-probability treatment weighted (IPTW) Cox proportional-hazards model to estimate the average treatment effect of the treated (ie, the MAG cohort) for the primary and secondary outcomes.[11]

Subgroup analyses

To address whether particular subgroups may particularly benefit (or not benefit) from multiple arterial grafting, a multivariable Cox proportional-hazards regression model that adjusted for the same baseline covariates as our propensity score model was employed to compare the primary outcome and the secondary outcome between MAG and SAG in various subgroups. First, we compared MAG and SAG in hospitals with high utilisation of MAG versus low utilisation of MAG by using the median utilisation rate to divide the 11 institutions. In addition, we compared MAG and SAG by tertiles of age groups (29–64 years, 65–74 years, and 75 years or older), left ventricular function (>50%, 35%–49%, <34%) and extent of coronary disease (two-vessel disease, three-vessel disease, left main disease). An interaction p value was obtained to determine whether there was a difference in treatment effect between the different subgroups.

For variables with ≤5% missing, we imputed using the mean for continuous outcome and the mode for binary/categorical outcomes. One categorical variable had missing data >5% (New York Heart Association classification); the missing data were imputed into the category 'unknown'. All analyses were conducted with SAS (V.9.4; SAS Institute, Cary, NC).

RESULTS

Over an 11-year period in Ontario, there were 10 915 patients with multivessel CAD that underwent multivessel CABG with at least one arterial graft of which 2961 underwent MAG (online supplemental figure 1). The rate of MAG utilisation was compared in women and men throughout the study period and while the utilisation rate did not increase with time in either sex, it was significantly higher in men compared with women (34% vs 28%, p<0.001, online supplemental figure 2). Prior to PS matching, patients undergoing MAG were younger (66.0 vs 68.9 years, p<0.001), had less cardiac comorbidities, lower

Table 1 Baseline characteristics and operative details before and after propensity score matching

	Before propensity score matching				After propensity score matching		
Variable	MAG n=2961	SAG n=7954	SMD	P value	MAG n=2446	SAG n=2446	SMD
Age	66.0 (9.9)	68.9 (9.3)	0.3	<0.0001	66.7 (9.9)	66.7 (9.8)	0
Body mass index	29.2 (5.8)	29.4 (6.1)	0.02	0.28	29.3 (6.0)	29.4 (5.9)	0.01
Hospital frailty risk score	3.2 (4.0)	3.8 (4.6)	0.15	<0.0001	3.4 (4.1)	3.2 (4.1)	0.04
Income quintile				0.03			
Lowest 1	667 (22.5%)	1986 (25.0%)	0.06		577 (23.6%)	597 (24.4%)	0.02
2	626 (21.1%)	1705 (21.4%)	0.01		529 (21.6%)	531 (21.7%)	0
3	608 (20.5%)	1612 (20.3%)	0.01		499 (20.4%)	459 (18.8%)	0.04
4	547 (18.5%)	1416 (17.8%)	0.02		437 (17.9%)	437 (17.9%)	0
Highest 5	513 (17.3%)	1235 (15.5%)	0.05		404 (16.5%)	422 (17.3%)	0.02
Hypertension	2346 (79.2%)	6682 (84.0%)	0.12	<0.0001	1960 (80.1%)	1969 (80.5%)	0.01
Diabetes	1373 (46.4%)	3812 (47.9%)	0.03	0.15	1144 (46.8%)	1136 (46.4%)	0.01
History of smoking				0.0003			
Current	598 (20.2%)	1546 (19.4%)	0.02		522 (21.3%)	520 (21.3%)	0
Former	653 (22.1%)	2050 (25.8%)	0.09		555 (22.7%)	571 (23.3%)	0.02
Never	1710 (57.8%)	4358 (54.8%)	0.06		1369 (56.0%)	1355 (55.4%)	0.01
CCS class				<0.0001			
0	148 (5.0%)	368 (4.6%)	0.02		113 (4.6%)	112 (4.6%)	0
1	173 (5.8%)	512 (6.4%)	0.02		153 (6.3%)	160 (6.5%)	0.01
2	504 (17.0%)	1178 (14.8%)	0.06		405 (16.6%)	390 (15.9%)	0.02
3	594 (20.1%)	1453 (18.3%)	0.05		471 (19.3%)	510 (20.9%)	0.04
4	112 (3.8%)	418 (5.3%)	0.07		102 (4.2%)	100 (4.1%)	0
ACS high risk	98 (3.3%)	502 (6.3%)	0.14		92 (3.8%)	94 (3.8%)	0
ACS intermediate risk	626 (21.1%)	1569 (19.7%)	0.04		525 (21.5%)	508 (20.8%)	0.02
ACS low risk	706 (23.8%)	1954 (24.6%)	0.02		585 (23.9%)	572 (23.4%)	0.01
New York Heart Association				<0.0001			
I	2347 (79.3%)	5188 (65.2%)	0.32		1865 (76.2%)	1860 (76.0%)	0
II	33 (1.1%)	156 (2.0%)	0.07		30 (1.2%)	33 (1.3%)	0.01
III	146 (4.9%)	504 (6.3%)	0.06		140 (5.7%)	131 (5.4%)	0.02
IV	209 (7.1%)	717 (9.0%)	0.07		191 (7.8%)	214 (8.7%)	0.03
Unknown	226 (7.6%)	1389 (17.5%)	0.3		220 (9.0%)	208 (8.5%)	0.02
Left ventricular function				0.31			
≥50%	2095 (70.8%)	5627 (70.7%)	0		1730 (70.7%)	1721 (70.4%)	0.01
35%–49%	605 (20.4%)	1634 (20.5%)	0		493 (20.2%)	512 (20.9%)	0.02
20%–34%	222 (7.5%)	620 (7.8%)	0.01		191 (7.8%)	188 (7.7%)	0
<20%	39 (1.3%)	73 (0.9%)	0.04		32 (1.3%)	25 (1.0%)	0.03
History of CHF	246 (8.3%)	989 (12.4%)	0.14	<0.0001	228 (9.3%)	225 (9.2%)	0
History of MI	524 (17.7%)	1630 (20.5%)	0.07	0.0011	458 (18.7%)	465 (19.0%)	0.01
Recent MI	1037 (35.0%)	3036 (38.2%)	0.07	<0.0001	879 (35.9%)	865 (35.4%)	0.01
PVD	300 (10.1%)	983 (12.4%)	0.07	0.0013	257 (10.5%)	272 (11.1%)	0.02
CVD	266 (9.0%)	837 (10.5%)	0.05	0.018	223 (9.1%)	217 (8.9%)	0.01
COPD	237 (8.0%)	865 (10.9%)	0.1	<0.0001	214 (8.7%)	204 (8.3%)	0.01
Serum creatinine (mg/dL)				<0.0001			
0–120	2754 (93.0%)	7104 (89.3%)	0.13		2260 (92.4%)	2263 (92.5%)	0
121–180	166 (5.6%)	536 (6.7%)	0.05		145 (5.9%)	137 (5.6%)	0.01
>180	41 (1.4%)	314 (3.9%)	0.16		41 (1.7%)	46 (1.9%)	0.02
Dialysis	22 (0.7%)	169 (2.1%)	0.12		22 (0.9%)	23 (0.9%)	0
Urgency status				<0.0001			
Elective	1338 (45.2%)	3065 (38.5%)	0.14		1047 (42.8%)	1056 (43.2%)	0.01
Semi-urgent	845 (28.5%)	2617 (32.9%)	0.09		728 (29.8%)	723 (29.6%)	0
Urgent	778 (26.3%)	2272 (28.6%)	0.05		671 (27.4%)	667 (27.3%)	0
Extent of coronary artery disease				<0.0001			
DVD with proximal LAD	408 (13.8%)	1180 (14.8%)	0.03		355 (14.5%)	341 (13.9%)	0.02
DVD without proximal LAD	255 (8.6%)	612 (7.7%)	0.03		211 (8.6%)	197 (8.1%)	0.02
TVD without LM	1466 (49.5%)	3333 (41.9%)	0.15		1130 (46.2%)	1132 (46.3%)	0

Continued

Table 1 Continued

Variable	Before propensity score matching				After propensity score matching		
	MAG n=2961	SAG n=7954	SMD	P value	MAG n=2446	SAG n=2446	SMD
LM±SVD/DVD	501 (16.9%)	1884 (23.7%)	0.17		464 (19.0%)	484 (19.8%)	0.02
LM with TVD	331 (11.2%)	945 (11.9%)	0.02		286 (11.7%)	292 (11.9%)	0.01
Off pump	1190 (40.2%)	893 (11.2%)	0.7	<0.0001	698 (28.5%)	693 (28.3%)	0
No of bypass grafts	3.4 (0.9)	3.1 (0.8)	0.35	<0.0001	3.3 (0.9)	3.3 (0.9)	0.02
No of arterial grafts	2.3 (0.52)	1.0 (0.0)	3.49	<0.0001	2.3 (0.5)	1.0 (0.0)	3.41
Radial artery use	1974 (66.7%)	248 (3.1%)	1.79	<0.001	1513 (61.9%)	166 (6.8%)	1.42

ACS, acute coronary syndrome; CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disorder; CVD, cerebrovascular disease; DVD, double-vessel disease; LAD, left anterior descending artery; LM, left main; MAG, multiple arterial grafting; MI, myocardial infarction; PVD, peripheral vascular disease; SAG, single arterial grafting; SMD, standardised mean difference; SVD, single-vessel disease; TVD, triple-vessel disease.

body mass index and better renal function compared with SAG patients (table 1). After propensity score matching, baseline characteristics were similar in 2446 well-matched pairs (83% of MAG patients were matched to a SAG patient) and all SMDs were <0.10, denoting acceptable balance between groups (table 1). Moreover, 76.9% of patients had left main disease and/or triple-vessel disease while the remainder had two-vessel disease including LAD with or without proximal LAD involvement. The mean number of grafts performed was similar for both groups, 3.3±0.9. Radial grafts were used in 62% of patients in the MAG cohort and the mean number of arterial grafts in the MAG group was 2.3±0.5. Finally, we compared patients who were PS matched to those who were not matched (online supplemental table 1) and found that PS-matched patients were younger and had more comorbidities compared with those who were not matched.

Early outcomes in propensity score–matched patients

In the PS-matched patients, there was no significant difference in early mortality (MAG: 1.6% vs SAG: 1.8%, p=0.44) between MAG and SAG. Similarly, there was no significant difference in in-hospital complications of MI (MAG 1.3% vs SAG 1.6%, p=0.47) or stroke (1.1% vs 1.1%, p=0.79) between MAG and SAG. Readmission for sternal complications was higher at 1 year in the MAG group (MAG: 1.5% vs SAG: 0.74%, p=0.009). Crude and PS-matched early outcomes are presented in table 2.

Late outcomes

The median follow-up was 5.0 years (IQR 2.6–7.8 years) and maximum follow-up was 11.0 years. Here, we present the results for the PS-matched patients. The use of MAG was associated with longer survival at 10 years (figure 1—MAG: 70.7% vs SAG: 67.3%, HR 0.85, 95% CI 0.74 to 0.98). Freedom from MACCE at 10 years was also higher in the MAG group (figure 2—MAG: 57.0% vs SAG: 50.6%, HR 0.85, 95% CI 0.76 to 0.95). After accounting for death as a competing risk, the incidence of MI at 10 years was not statistically different between MAG and SAG (online supplemental figure 3—MAG: 11.3% vs SAG: 16.3%, HR 0.82, 95% CI 0.67 to 1.00), but the incidence of repeat revascularisation was lower with MAG (online supplemental figure 4—MAG: 13.3% vs SAG: 16.2% at 10 years, HR 0.77, 95% CI 0.64 to 0.93). The incidence of stroke was similar between MAG and SAG (online supplemental figure 5—MAG: 6.7% vs SAG: 6.9% at 10 years, HR 1.03, 95% CI 0.76 to 1.39).

In the full sample, before propensity score matching, 10-year survival was significantly higher in MAG patients compared with SAG patients (online supplemental figure 6—MAG: 72.1% vs SAG: 62.5%, p<0.001). Similarly, freedom from MACCE was also significantly higher at 10 years with MAG compared with SAG (online supplemental figure 7—MAG: 58.4% vs SAG: 48.5%, p<0.001). All long-term outcomes before and after PS matching can be found in online supplemental tables 2 and 3, respectively.

Sensitivity analysis: inverse probability treatment weighting

Propensity scores that included 21 baseline characteristics and institutions were developed and used to estimate the average treatment effect of the treated in an IPTW Cox proportional-hazards model. IPTW yielded two comparable groups (online supplemental table 4) with SMD <0.10, denoting acceptable balance. Findings for the primary outcome of long-term all-cause mortality were robust and favoured MAG (online supplemental figure 8—MAG: 72.1% vs SAG: 68.4% at 10 years) with a HR 0.84 (95% CI 0.71 to 0.98) over the entire study period. Similarly, the secondary outcome of freedom from MACCE at 10 years was also significantly better with MAG in the IPTW model (online supplemental figure 9—MAG: 58.4% vs SAG: 55.5%, HR 0.87, 95% CI 0.76 to 0.99).

Subgroup analyses

There were no significant subgroup differences (online supplemental figure 10) when the primary and secondary outcome

Table 2 Early outcomes before and after propensity score matching

	Before propensity score matching			After propensity score matching		
	MAG n=2961	SAG n=7954	P value	MAG n=2446	SAG n=2446	P value
Early death	43 (1.5%)	213 (2.7%)	0.0002	38 (1.6%)	45 (1.8%)	0.44
In-hospital stroke	27 (0.9%)	134 (1.7%)	0.003	26 (1.1%)	28 (1.1%)	0.79
In-hospital acute MI	35 (1.2%)	86 (1.1%)	0.65	32 (1.3%)	38 (1.6%)	0.47
Sternal complication within 1 year	37 (1.2%)	63 (0.8%)	0.03	37 (1.5%)	18 (0.74%)	0.009

MAG, multiple arterial grafting; MI, myocardial infarction; SAG, single arterial grafting.

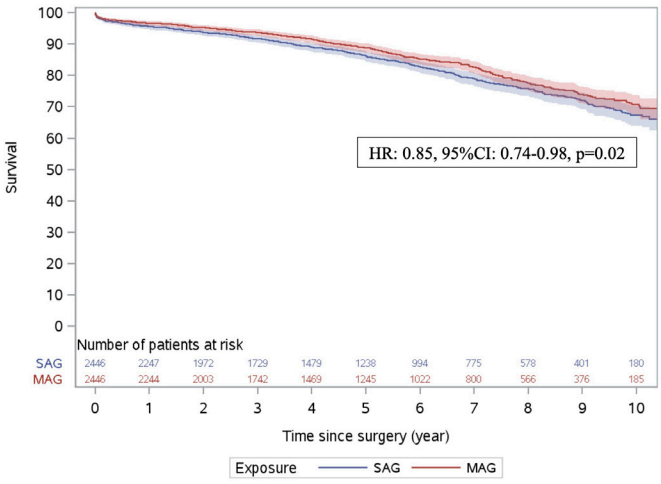

Figure 1 Kaplan-Meier curves for long-term survival. Survival was compared between multiple arterial grafting (MAG) vs single arterial grafting (SAG) after propensity score matching in patients multivessel coronary artery disease. The shaded region around the curve represents the 95% CI.

was compared between high versus low MAG utilisation hospitals (interaction p=0.19), age groups (interaction p=0.40), left ventricular function (interaction p=0.73) and extent of CAD (interaction p=0.16).

DISCUSSION

The use of MAG in women was associated with similar early mortality and significantly higher survival, greater freedom from MACCE and repeat revascularisation compared with the use of SAG. However, the risk of sternal complications was higher at 1 year in the MAG group in PS-matched patients. Importantly, we noted in our analysis which encompassed all women with multivessel CAD undergoing multivessel coronary artery bypass grafting performed in Ontario, 28% of women underwent multiple arterial grafting, and the rate of MAG utilisation did not increase from 2008 to 2019.

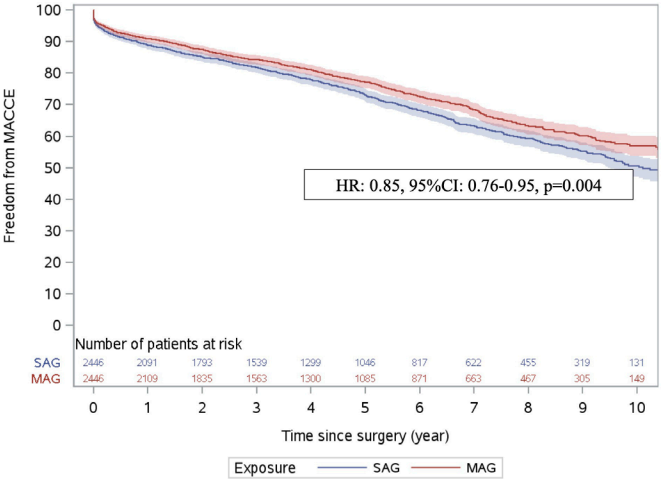

Figure 2 Kaplan-Meier curves for freedom from major adverse cardiac and cerebrovascular events (MACCEs). Freedom from MACCE was compared between multiple arterial grafting (MAG) vs single arterial grafting (SAG) after propensity score matching in patients multivessel coronary artery disease. The shaded region around the curve represents the 95% CI.

Jabagi and colleagues looked at the impact of sex on the choice of revascularisation strategy in patients undergoing CABG at the University of Ottawa Heart Institute and found that male sex was associated with increased bilateral IMA (BIMA) usage.[12] Similar findings have been observed at the Cleveland Clinic where women were found to receive fewer BIMA grafts (4.8% vs 12%, p<0.0001) and total arterial grafting was also less common in women (8.4% vs 9.3%, p=0.005).[13] Consistent with the literature, we found that the utilisation of MAG was significantly higher in men compared with women despite similar coronary anatomy over the study period. These findings suggest that women may be less likely to get MAG compared with men, despite similar risk profiles.

There may be several reasons for potential under-utilisation of multiple arterial grafts in women compared with equivalent men seen in the previously described studies. In Ontario, there are data to suggest that women are referred later for CABG and present with more advanced disease at the time of CABG.[6 14] In addition, women on average have smaller native coronary vessels which may be more technically challenging to graft.[15 16] Taken together, understanding these factors of delayed diagnosis, more urgent/emergent surgery, and smaller native coronary vessels, may help explain why the utilisation of multiple arterial grafts may be lower in women.

However, the primary reason for the underutilization of bilateral IMA grafting seen in the literature may be related to the fear of increased risk for sternal complications in women. Gatti and colleagues created a deep sternal wound infection predictive risk score for those undergoing bilateral IMA grafting where female sex was the strongest predictor, and was associated with a threefold increase in deep sternal wound infection.[17] Results from the ART trial have shown that pedicled BIMA use was associated with an almost twofold risk in sternal complications with female sex as independent risk factor.[18] However, the key to safely employing BIMA grafting may be related in part with the harvesting technique. As such, multiple studies have showed that the use of skeletonised BIMA does not increase the risk of sternal complication.[18 19] Recent data from the representative Society of Thoracic Surgeons' Adult Cardiac Surgery Database suggests that in patients undergoing BIMA grafting, skeletonisation of both IMAs is employed less than half the time and typically performed by surgeons more experienced in BIMA grafting.[20]

The impact of arterial grafting in women is not well known in the literature as they remain grossly under-represented in clinical trials, and as such, this may preclude generalisation of the findings to women.[1 2] Lawton and associates have shown greater 5-year survival with radial artery use in 294 propensity score–matched pairs of women undergoing CABG.[21] The incremental long-term benefit of a second arterial conduit was recently studied in Ontario by Rubens and colleagues and authors found that a second arterial conduit was associated with an incremental 4.0% improvement in 9-year survival in women while only 0.9% in men.[22] Recently, Gaudino and colleagues have shown that the radial artery is superior to saphenous vein graft as the second conduit in a patient-level meta-analysis of six clinical trials that showed improved patency and lower late MACCEs with radial artery use at median 10-year follow-up.[23] Interestingly, the use of the radial artery may have greater benefits in women compared with men in a subgroup analysis (HR 0.23 vs HR 0.83, interaction p<0.01).[1] Furthermore, given that at the population level, women have higher average life expectancy than men, arterial grafting should be strongly considered in women undergoing CABG.[6] Nonetheless, despite the plethora of supportive observational studies, we acknowledge that there has been no single

RCT that has demonstrated a survival benefit to a multiple arterial grafting strategy, including the recently published ART trial, which is the largest trial to date and the only trial powered for mortality.[2] However, the ART trial has been criticised for a high cross-over rate from BIMA to single IMA in the exposure arm, and a high utilisation of a second arterial graft in the control group. The on-going Randomization of Single vs Multiple Arterial Grafts (ROMA) trial, which plans to enrol 4300 patients, is poised to definitively answer the question regarding the effectiveness of multiple arterial grafting.[24]

Limitations

This study must be interpreted in the context of some limitations. First, these findings are subject to the usual limitations around the retrospective observational administrative and clinical registry study designs. Despite extensive adjustment for baseline characteristics using propensity score matching, we acknowledge that unknown or unmeasured confounders may still bias the treatment allocation of patients to either strategy. Furthermore, we note that propensity-matched patients differed in characteristics compared with those who were not matched; PS-matched patients were younger and had less comorbidities. Thus, whether MAG is superior to SAG in an older and less healthy population remains uncertain. There is limitation around the granularity of available data, for example, we do not have detailed information regarding the target vessel size, the degree of significant stenosis for each of the grafted vessels, or whether grafts were placed to the left and right coronary system. Finally, the median follow-up time was 5.0 years and longer follow-up of this cohort is necessary to better understand the late consequences of MAG versus SAG strategies.

CONCLUSION

Multiple arterial grafting was associated with significantly greater survival in women without increasing early mortality compared with SAG. However, the incidence of sternal complications was higher in women at 1 year and consideration regarding the optimal harvesting technique and arterial grafting strategy in women should be further delineated.

Key messages

What is already known on this subject?

- In observational studies that include mostly 80%–90% men, multiple arterial grafting is associated with greater long-term survival and event-free survival. However, whether this effect is consistent in women is not known.

What might this study add?

- In this propensity-matched cohort study of 2446 pairs of women undergoing coronary artery bypass grafting for multivessel coronary artery disease, multiple arterial grafting was associated with greater long-term survival and freedom from major adverse cardiac and cerebrovascular events compared with single arterial grafting.

How might this impact on clinical practice?

- The use of multiple arterial grafts should be considered in women with reasonable life expectancy requiring coronary artery bypass grafting for multivessel coronary artery disease.

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Contributors All authors participated in (1) conception and design or analysis and interpretation of data, or both; (2) drafting of the manuscript or revising it critically for important intellectual content; and (3) final approval of the manuscript submitted.

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Data availability statement Data may be obtained from a third party and are not publicly available. The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access (available at www.ices.on.ca/DAS). The full dataset creation plan and underlying analytic code are available from the authors on request, understanding that the computer programs may rely on coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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Supplemental Appendix

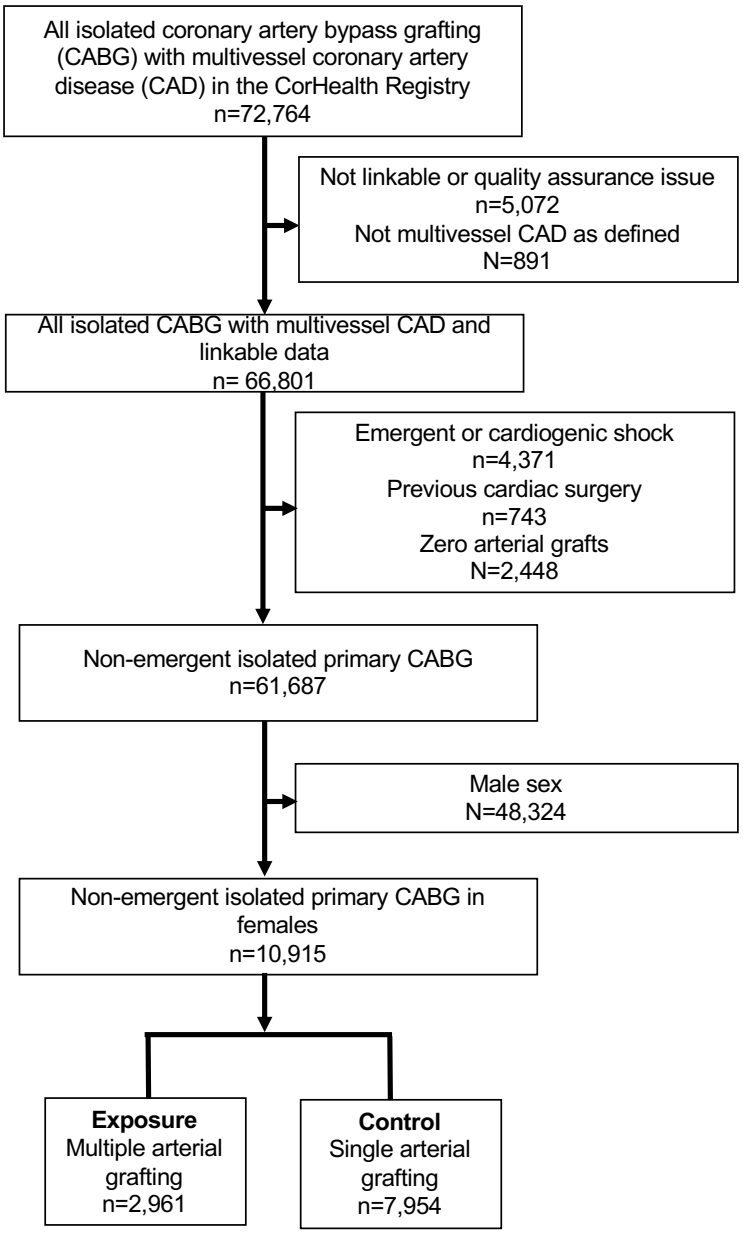
Variables entered into propensity score

1. Age
2. Body Mass Index
3. Hospital Frailty Risk Score
4. Income Quintile
5. Hypertension
6. Diabetes
7. History of smoking
8. CCS Class
9. NY Heart Association
10. Left ventricular function
11. History of CHF
12. History of MI
13. Recent MI
14. PVD
15. CVD
16. COPD
17. Creatinine Group
18. Dialysis
19. Urgency Status
20. Extent of coronary artery disease
21. Off Pump

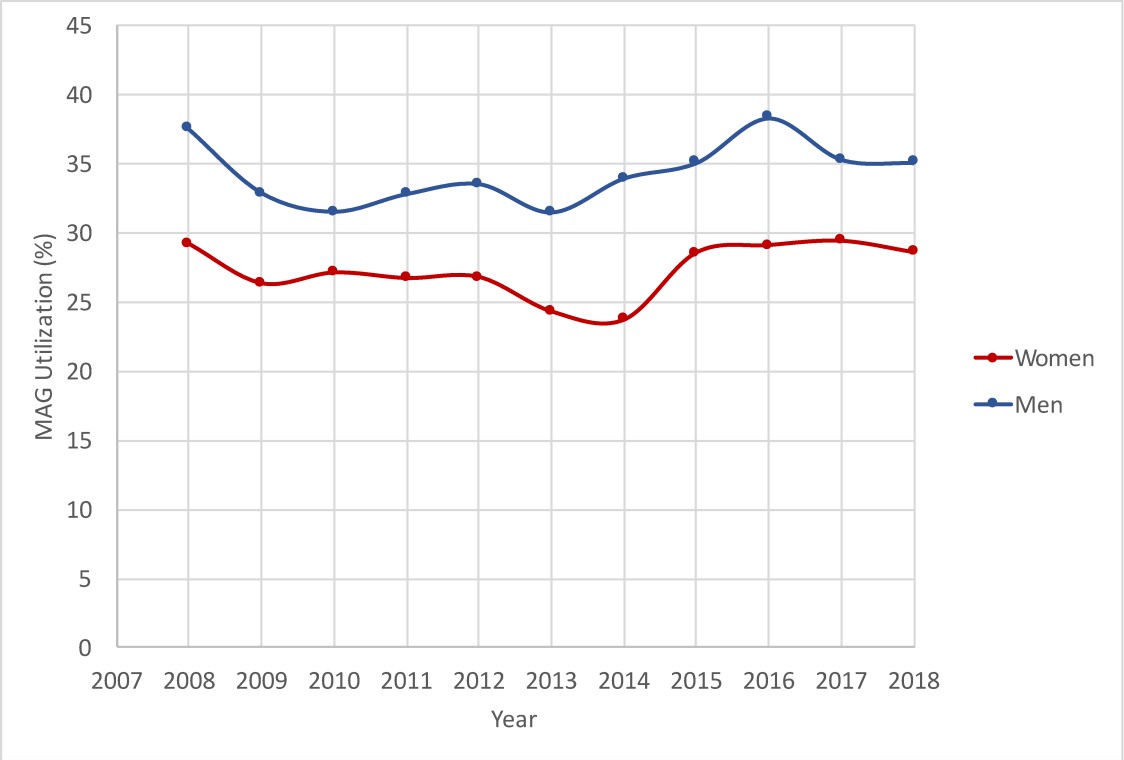
Codes for outcome ascertainment

	Database	Codes
Outcomes		
ICU length of stay	OHIP	Number of days that the following OHIP codes are continuously billed following index procedure: G400, G405 OR G557 (first day); G401, G406 OR G558 (days 2-30); G402, G407 OR G559 (after 31 days).
Hospital length of stay	CIHI-DAD	Number of days between index procedure and discharge date, subtracting the number of ALC days (ALC LOS). Discharge is defined as discharge/transfer to any non-hospital/non-acute care facility (DISCHDISP = 2, 3, 4, 5, 6, 7, 12).
Any stroke	CIHI-DAD	**ICD-10** I60.x I61.x I62.x I63.x, I64.x, H34.1 (excluding I63.6)
Acute myocardial infarction	CIHI-DAD	**ICD-10** I21.x, I22.x
Sternal complications	CIHI-DAD	**CCI:** 1SK.73, 1SK74, 1SK80, 1SK87, 1SY80LAXXG
Coronary revascularization	CIHI-DAD	**CCI** 1IJ50x, 1IJ54x, 1IJ57GQ, 1IJ76x
- Percutaneous coronary intervention	CIHI-DAD	CCI codes: 1IJ50, 1IJ54, 1IJ57GQ
- Coronary artery bypass graft surgery	CIHI-DAD	CCI code 1IJ76

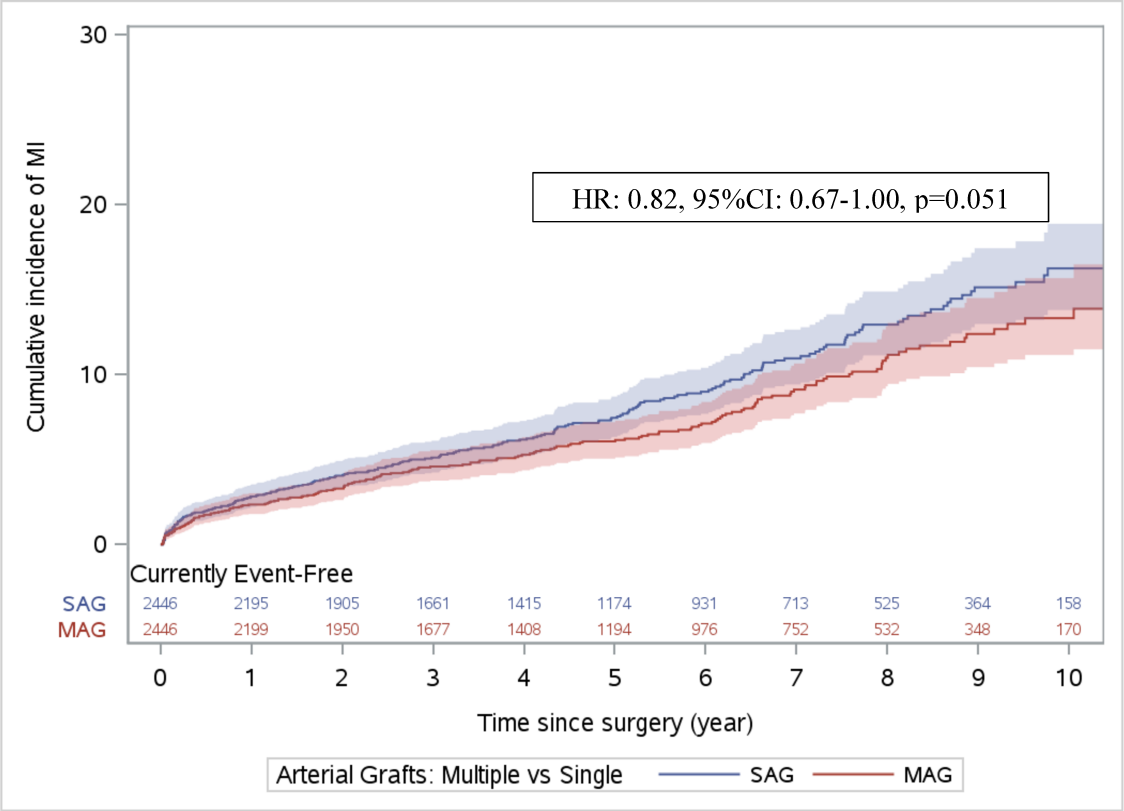
Supplemental Figures



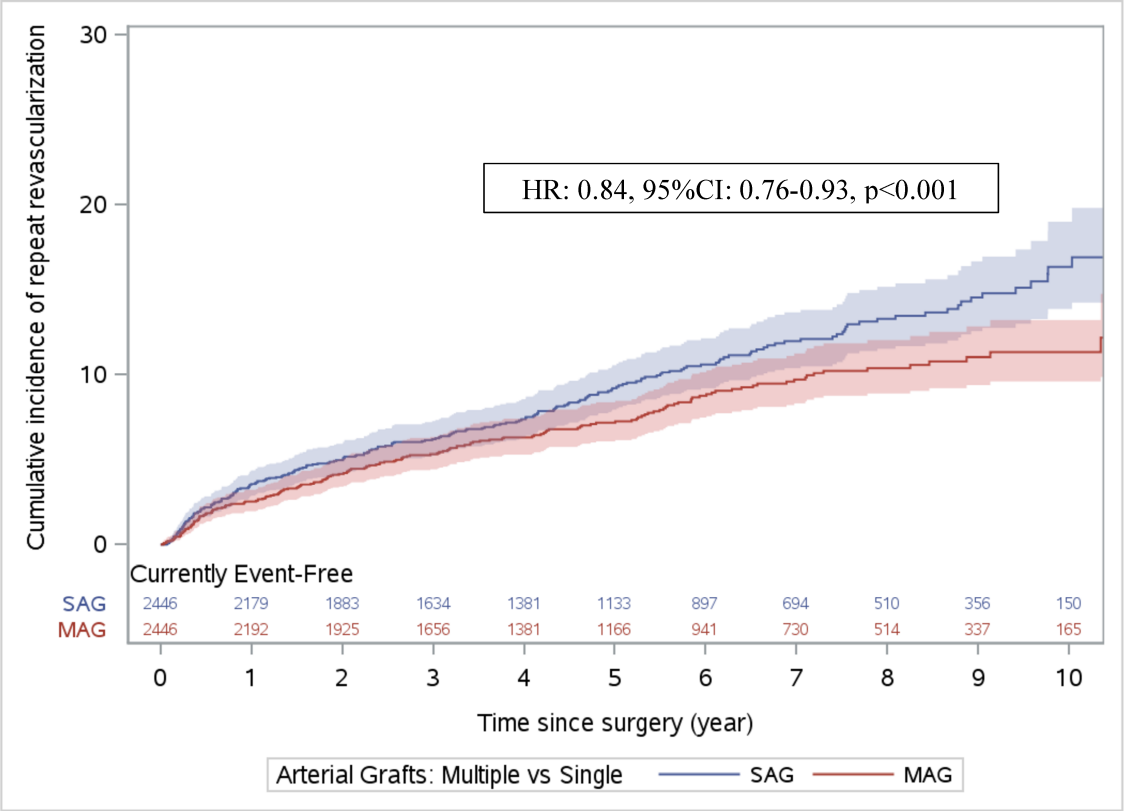
Supplemental Figure 1. Patient flow diagram for cohort derivation.



Supplemental Figure 2. Time trend for multiple arterial grafting (MAG) utilization in women (red) and men (blue) with multivessel coronary artery disease. Linear regression of MAG utilization by year of procedure was not significant in women (p=0.47) or men (p=0.35) although the utilization was higher in men compared to women (34% vs 28%, p<0.001) over the entire study period.

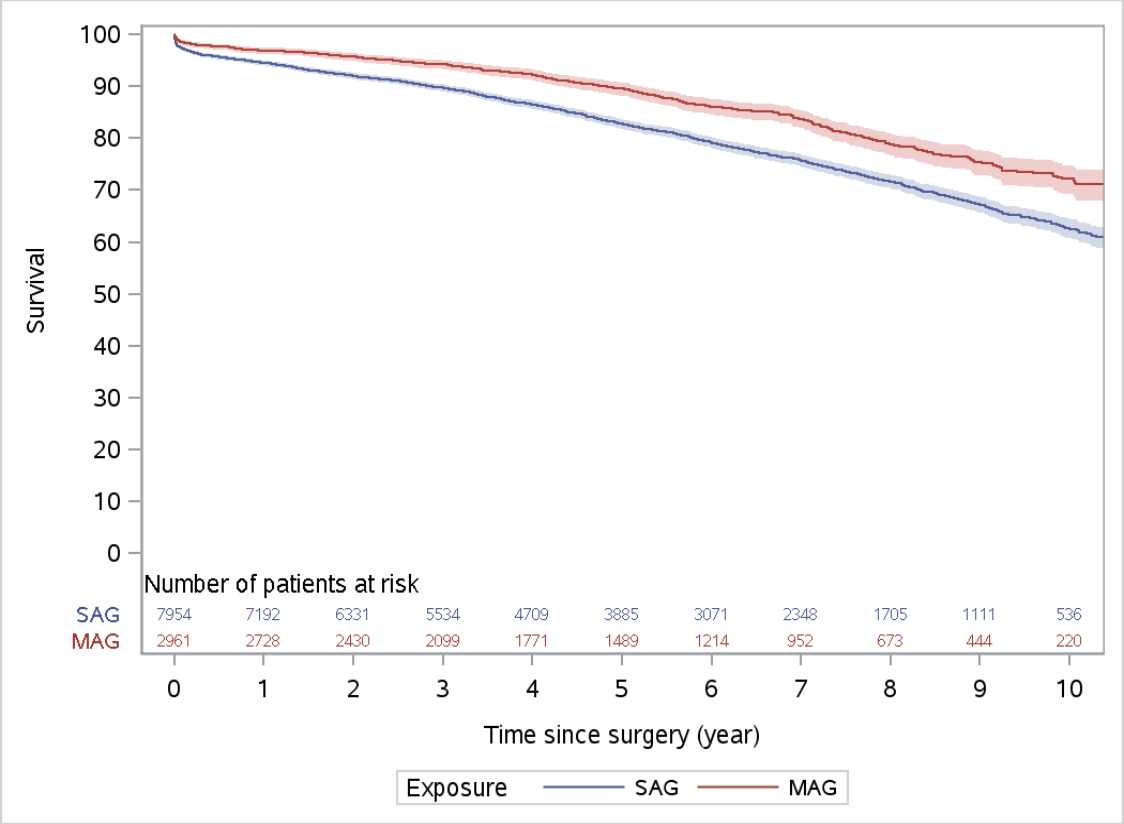


Supplemental Figure 3. Cumulative incidence curves for acute myocardial infarction was compared between multiple arterial grafting (MAG) versus single arterial grafting (SAG) after propensity score matching in patients multivessel coronary artery disease and adjusting for death as a competing risk. The shaded region around the curve represents the 95% confidence interval.

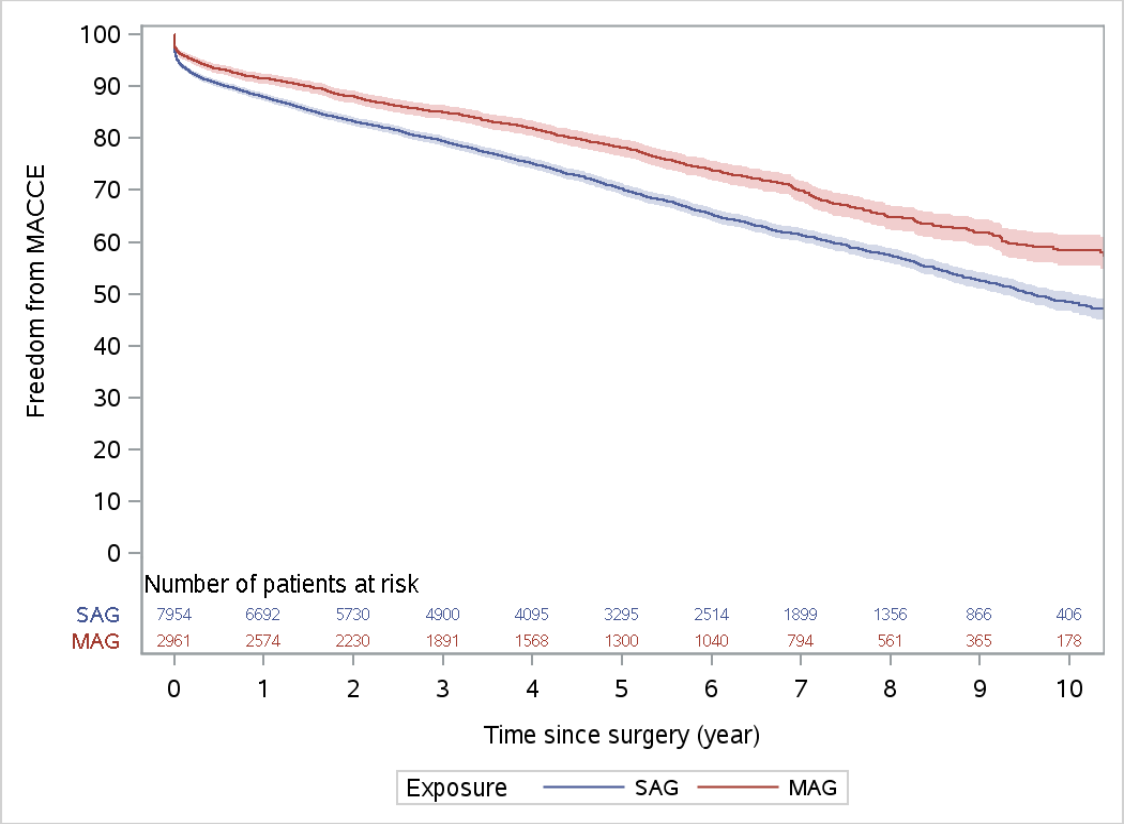


Supplemental Figure 4. Cumulative incidence curves for repeat revascularization was compared between multiple arterial grafting (MAG) versus single arterial grafting (SAG) after propensity score matching in patients multivessel coronary artery disease and adjusting for death as a competing risk. The shaded region around the curve represents the 95% confidence interval.

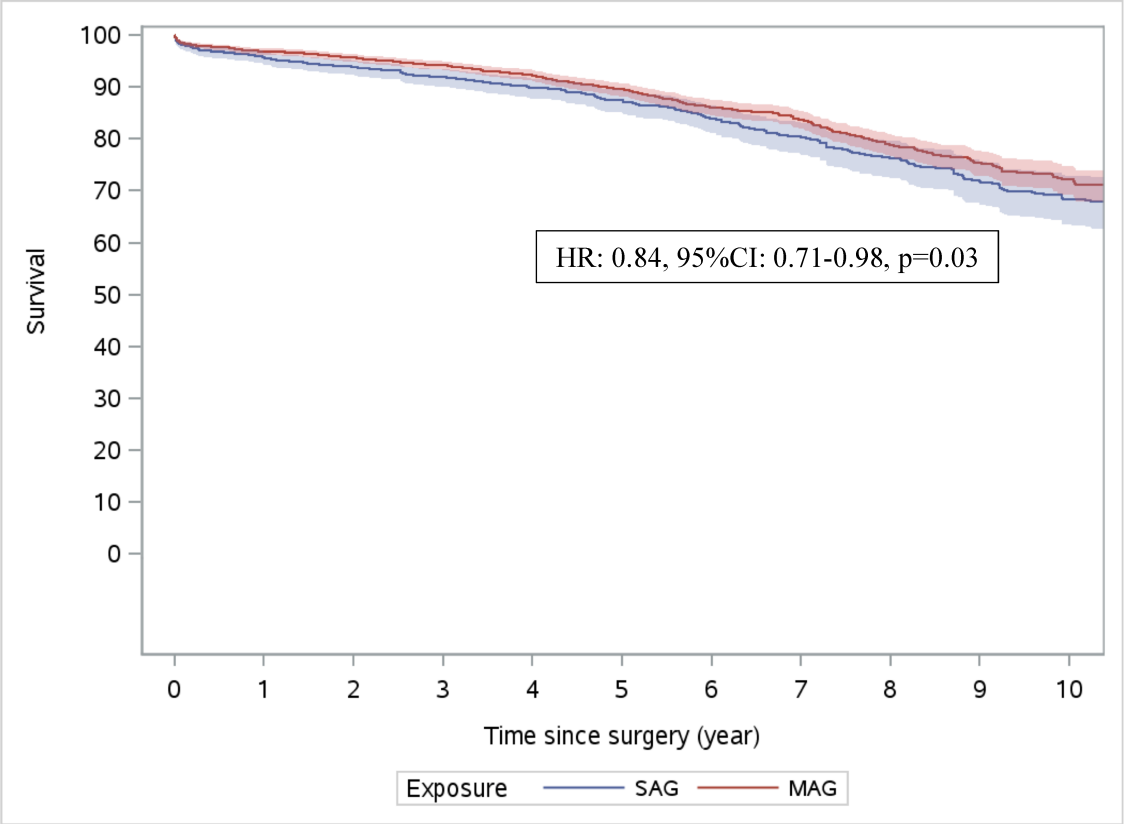
Supplemental Figure 5. Cumulative incidence curves stroke was compared between multiple arterial grafting (MAG) versus single arterial grafting (SAG) after propensity score matching in patients multivessel coronary artery disease and adjusting for death as a competing risk. The shaded region around the curve represents the 95% confidence interval.



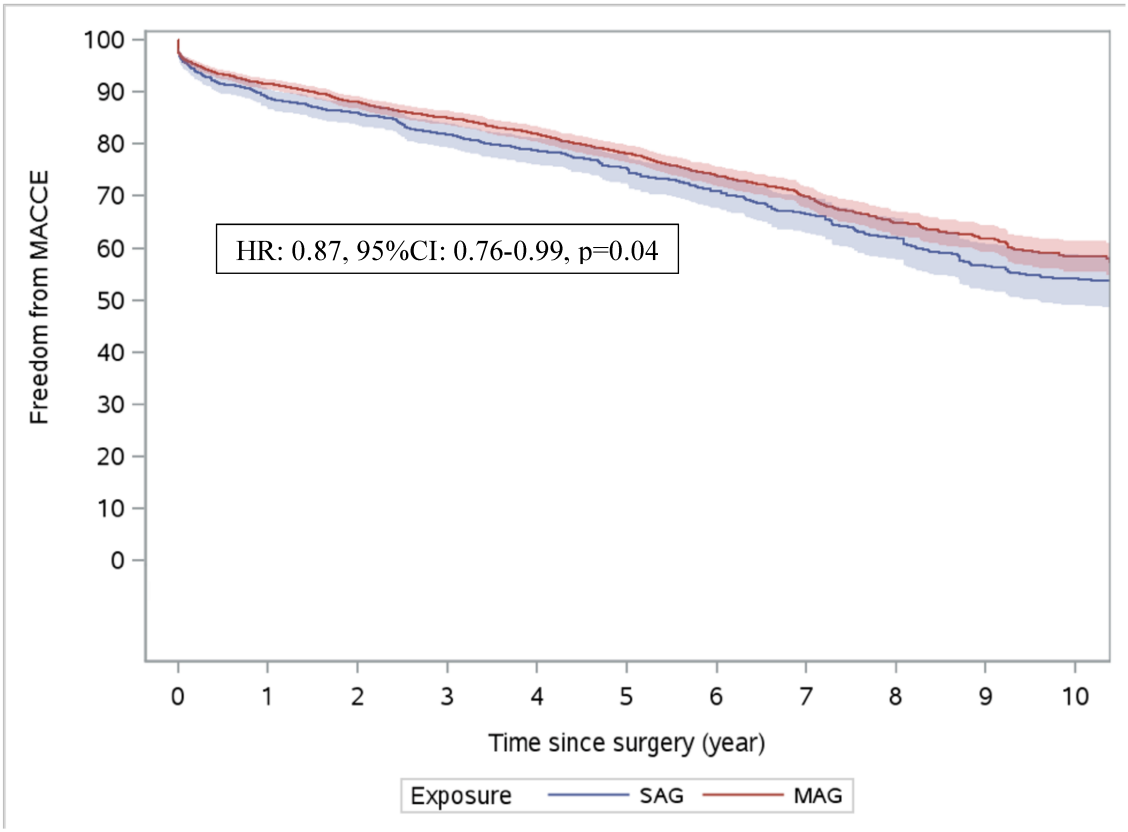
Supplemental Figure 6. Kaplan-Meier curves for survival. Survival was compared between multiple arterial grafting (MAG) versus single arterial grafting (SAG) before propensity score matching in patients multivessel coronary artery disease. The shaded region around the curve represents the 95% confidence interval.



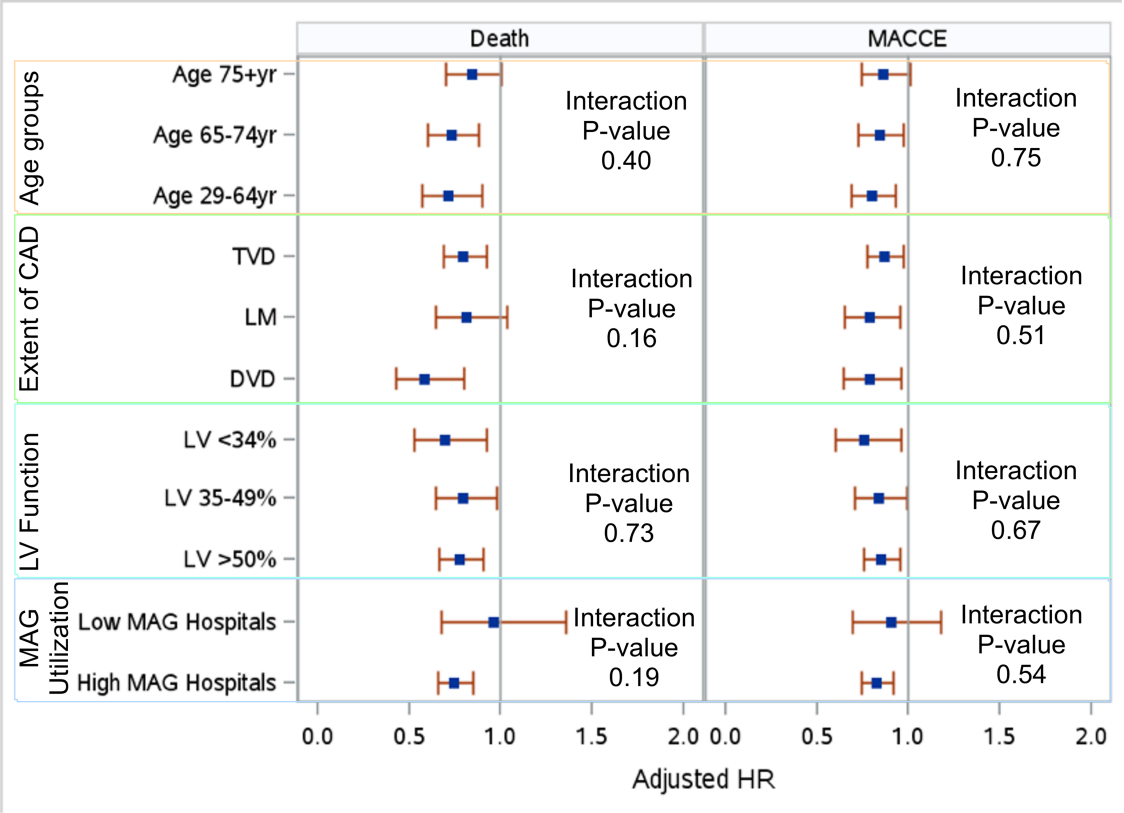
Supplemental Figure 7. Kaplan-Meier curves for freedom from major adverse cardiac and cerebrovascular events (MACCE). Freedom from MACCE was compared between multiple arterial grafting (MAG) versus single arterial grafting (SAG) before propensity score matching in patients multivessel coronary artery disease. The shaded region around the curve represents the 95% confidence interval.



Supplemental Figure 8. Weighted Kaplan-Meier curves for survival. Survival was compared between multiple arterial grafting (MAG) versus single arterial grafting (SAG) after inverse-probability of treatment weighting in patients multivessel coronary artery disease. The shaded region around the curve represents the 95% confidence interval.



Supplemental Figure 9. Weighted Kaplan-Meier curves for freedom from major adverse cardiac and cerebrovascular events (MACCE). Freedom from MACCE was compared between multiple arterial grafting (MAG) versus single arterial grafting (SAG) after inverse-probability of treatment weighting in patients multivessel coronary artery disease. The shaded region around the curve represents the 95% confidence interval.



Supplemental Figure 10. Subgroup analysis comparing multiple arterial grafting (MAG) versus single arterial grafting (SAG) for the primary outcome of death and the secondary outcome of major adverse cardiac and cerebrovascular events (MACCE) in a multivariable Cox-proportional hazards model. The adjusted hazard ratio (HR) is presented with >1.0 indicating harm with MAG and <1.0 indicating benefit for MAG. CAD, coronary artery disease, LV, left ventricular

Supplemental Tables

Supplemental Table 1. Baseline characteristics of propensity score (PS) matched patients and patients that were not matched

Variable	PS Matched	Not Matched	Overall	SMD	P-value
	N=4,892	N=6,023	N=10,915		
Age	66.7 (9.8)	69.3 (9.1)	68.1 (9.6)	0.27	<.0001
Body Mass Index	29.4 (5.9)	29.3 (6.1)	29.3 (6.0)	0	0.88
Hospital Frailty Risk Score	3.3 (4.1)	3.9 (4.7)	3.6 (4.4)	0.15	<.0001
Income Quintile					<.0001
Lowest 1	1,174 (24.0%)	1,479 (24.6%)	2,653 (24.3%)	0.01	
2	1,060 (21.7%)	1,271 (21.1%)	2,331 (21.4%)	0.01	
3	958 (19.6%)	1,262 (21.0%)	2,220 (20.3%)	0.03	
4	874 (17.9%)	1,089 (18.1%)	1,963 (18.0%)	0.01	
Highest 5	826 (16.9%)	922 (15.3%)	1,748 (16.0%)	0.04	
Hypertension	3,929 (80.3%)	5,099 (84.7%)	9,028 (82.7%)	0.11	<.0001
Diabetes	2,280 (46.6%)	2,905 (48.2%)	5,185 (47.5%)	0.03	0.0909
History of smoking					<.0001
Current	1,042 (21.3%)	1,102 (18.3%)	2,144 (19.6%)	0.08	
Former	1,126 (23.0%)	1,577 (26.2%)	2,703 (24.8%)	0.07	
Never	2,724 (55.7%)	3,344 (55.5%)	6,068 (55.6%)	0	
CCS Class					<.0001
0	225 (4.6%)	291 (4.8%)	516 (4.7%)	0.01	
1	313 (6.4%)	372 (6.2%)	685 (6.3%)	0.01	

2	795 (16.3%)	887 (14.7%)	1,682 (15.4%)	0.04	
3	981 (20.1%)	1,066 (17.7%)	2,047 (18.8%)	0.06	
4	202 (4.1%)	328 (5.4%)	530 (4.9%)	0.06	
ACS High Risk	186 (3.8%)	414 (6.9%)	600 (5.5%)	0.14	
ACS Intermediate Risk	1,033 (21.1%)	1,162 (19.3%)	2,195 (20.1%)	0.05	
ACS Low Risk	1,157 (23.7%)	1,503 (25.0%)	2,660 (24.4%)	0.03	
NY Heart Association					<.0001
I	3,725 (76.1%)	3,810 (63.3%)	7,535 (69.0%)	0.28	
II	63 (1.3%)	126 (2.1%)	189 (1.7%)	0.06	
III	271 (5.5%)	379 (6.3%)	650 (6.0%)	0.03	
IV	405 (8.3%)	521 (8.7%)	926 (8.5%)	0.01	
Unknown	428 (8.7%)	1,187 (19.7%)	1,615 (14.8%)	0.32	
Left ventricular function					0.6283
20% - 34 %	379 (7.7%)	463 (7.7%)	842 (7.7%)	0	
35% - 49%	1,005 (20.5%)	1,234 (20.5%)	2,239 (20.5%)	0	
<20%	57 (1.2%)	55 (0.9%)	112 (1.0%)	0.02	
>=50%	3,451 (70.5%)	4,271 (70.9%)	7,722 (70.7%)	0.01	<.0001
History of CHF	453 (9.3%)	782 (13.0%)	1,235 (11.3%)	0.12	0.04
History of MI	923 (18.9%)	1,231 (20.4%)	2,154 (19.7%)	0.04	0.0012
Recent MI	1,744 (35.7%)	2,329 (38.7%)	4,073 (37.3%)	0.06	0.0059

PVD	529 (10.8%)	754 (12.5%)	1,283 (11.8%)	0.05	0.0005
CVD	440 (9.0%)	663 (11.0%)	1,103 (10.1%)	0.07	<.0001
COPD	418 (8.5%)	684 (11.4%)	1,102 (10.1%)	0.09	<.0001
Creatinine Group					<.0001
0-120	4,523 (92.5%)	5,335 (88.6%)	9,858 (90.3%)	0.13	
121-180	282 (5.8%)	420 (7.0%)	702 (6.4%)	0.05	
>180	87 (1.8%)	268 (4.4%)	355 (3.3%)	0.15	
Dialysis	45 (0.9%)	146 (2.4%)	191 (1.7%)	0.12	<.0001
Urgency Status					<.0001
Elective	2,103 (43.0%)	2,300 (38.2%)	4,403 (40.3%)	0.1	
SemiUrgent	1,451 (29.7%)	2,011 (33.4%)	3,462 (31.7%)	0.08	
Urgent	1,338 (27.4%)	1,712 (28.4%)	3,050 (27.9%)	0.02	
Extent of coronary artery disease					0.11
DVD with proximal LAD	696 (14.2%)	892 (14.8%)	1,588 (14.5%)	0.02	
DVD without proximal LAD	408 (8.3%)	459 (7.6%)	867 (7.9%)	0.03	
LM ± SVD/DVD	948 (19.4%)	1,437 (23.9%)	2,385 (21.9%)	0.11	
LM with TVD	578 (11.8%)	698 (11.6%)	1,276 (11.7%)	0.01	
TVD without LM	2,262 (46.2%)	2,537 (42.1%)	4,799 (44.0%)	0.08	
Off Pump	1,391 (28.4%)	692 (11.5%)	2,083 (19.1%)	0.43	<.0001

ACS, acute coronary syndrome, CCS, Canadian Cardiovascular Society, CHF, congestive heart failure, COPD, chronic obstructive pulmonary disorder, CVD, cerebrovascular disease, DVD, double vessel disease, LAD, left anterior descending artery, LM, left main, MI, myocardial

infarction, PVD, peripheral vascular disease, SVD, single vessel disease, TVD, triple vessel disease

Supplemental Table 2. Long-term outcomes before and after propensity score matching

	Year	MAG	SAG
Survival	1	96.9% (95%CI: 96.2%-97.4%)	94.5% (95%CI: 94%-95%)
	5	89.5% (95%CI: 88.2%-90.7%)	82.8% (95%CI: 81.8%-83.7%)
	10	72.1% (95%CI: 69.2%-74.8%)	62.5% (95%CI: 60.6%-64.4%)
	Overall	HR: 0.65, 95%CI: (0.59 - 0.73)	
Freedom from MACCE	1	91.4% (95%CI: 90.4%-92.4%)	87.9% (95%CI: 87.2%-88.6%)
	5	78.2% (95%CI: 76.4%-79.8%)	70.2% (95%CI: 69.1%-71.3%)
	10	58.4% (95%CI: 55.5%-61.3%)	48.5% (95%CI: 46.7%-50.4%)
	Overall	HR: 0.73, 95%CI: (0.67 - 0.79)	
Acute MI	1	2.3% (95%CI: 1.8%-2.8%)	3.1% (95%CI: 2.8%-3.5%)
	5	6% (95%CI: 5.1%-7%)	8.2% (95%CI: 7.5%-8.9%)
	10	12.6% (95%CI: 10.7%-14.8%)	17% (95%CI: 15.5%-18.6%)
	Overall	HR: 0.74, 95%CI: (0.63 - 0.87)	
Repeat Revascularization	1	2.4% (95%CI: 1.9%-3%)	2.9% (95%CI: 2.6%-3.3%)
	5	7.1% (95%CI: 6.1%-8.2%)	8% (95%CI: 7.3%-8.7%)
	10	11.5% (95%CI: 9.9%-13.3%)	13.6% (95%CI: 12.3%-14.9%)
	Overall	HR: 0.92, 95%CI: (0.79 - 1.07)	
Stroke	1	0.7% (95%CI: 0.4%-1%)	0.8% (95%CI: 0.6%-1%)
	5	3.2% (95%CI: 2.5%-4%)	3.9% (95%CI: 3.4%-4.4%)
	10	6.5% (95%CI: 5.1%-8.3%)	8.4% (95%CI: 7.3%-9.6%)
	Overall	HR: 0.79, 95%CI: (0.63 - 0.99)	

MACCE, major cardiac and cerebrovascular events (composite of time to first event for death, acute MI, repeat revascularization, or stroke). MAG, multiple arterial grafting, MI, myocardial infarction, SAG, single arterial grafting

For survival and freedom from MACCE, Kaplan-Meier estimates are shown. For Acute MI, repeat revascularization, and stroke, the cumulative incidence estimate are shown.

Supplemental Table 3. Long-term outcomes after propensity score matching

	Year	MAG	SAG
Survival	1	96.6% (95%CI: 95.8%-97.3%)	95.5% (95%CI: 94.6%-96.3%)
	5	88.8% (95%CI: 87.3%-90.2%)	86.2% (95%CI: 84.6%-87.7%)
	10	70.7% (95%CI: 67.5%-73.7%)	67.3% (95%CI: 64%-70.4%)
	Overall	HR: 0.85, 95%CI: (0.75 - 0.98)	
Freedom from MACCE	1	90.8% (95%CI: 89.6%-91.9%)	88.8% (95%CI: 87.5%-90%)
	5	77.2% (95%CI: 75.2%-79%)	73.1% (95%CI: 71.1%-75%)
	10	57% (95%CI: 53.8%-60.1%)	50.6% (95%CI: 47.3%-53.8%)
	Overall	HR: 0.85, 95%CI: (0.76 - 0.93)	
Acute MI	1	2.5% (95%CI: 2%-3.2%)	3.6% (95%CI: 2.9%-4.4%)
	5	7.2% (95%CI: 6.1%-8.4%)	9.2% (95%CI: 7.9%-10.6%)
	10	11.3% (95%CI: 9.6%-13.2%)	16.3% (95%CI: 13.9%-19%)
	Overall	HR: 0.82, 95%CI: (0.67 – 1.00)	
Repeat Revascularization	1	2.4% (95%CI: 1.8%-3%)	2.8% (95%CI: 2.2%-3.6%)
	5	6.1% (95%CI: 5.1%-7.2%)	7.5% (95%CI: 6.3%-8.7%)
	10	13.3% (95%CI: 11.2%-15.7%)	16.2% (95%CI: 13.8%-18.9%)
	Overall	HR: 0.79, 95%CI: (0.65 - 0.94)	
Stroke	1	0.7% (95%CI: 0.4%-1.1%)	0.6% (95%CI: 0.4%-1%)
	5	3.4% (95%CI: 2.6%-4.3%)	3.4% (95%CI: 2.6%-4.3%)
	10	6.7% (95%CI: 5.1%-8.6%)	6.9% (95%CI: 5.3%-8.9%)

	Overall	HR: 1.03, 95%CI: (0.76 - 1.38)

MACCE, major cardiac and cerebrovascular events (composite of time to first event for death, acute MI, repeat revascularization, or stroke). MAG, multiple arterial grafting, MI, myocardial infarction, SAG, single arterial grafting

For survival and freedom from MACCE, Kaplan-Meier estimates are shown. For Acute MI, repeat revascularization, and stroke, the cumulative incidence estimate are shown.

Supplemental Table 4. Baseline characteristics before and after inverse probability of treatment weighting (IPTW)

	Before IPTW			After IPTW		
Variable	**MAG**	**SAG**	**SMD**	**MAG**	**SAG**	**SMD**
Age	66.0	68.9	0.30	66.0	65.5	0.050
Body Mass Index	29.2	29.4	0.020	29.2	29.3	0.010
Hospital Frailty Risk Score	3.2	3.8	0.150	3.2	3.3	0.030
Income Quintile						
Lowest 1	22.5%	25.0%	0.060	22.5%	24.0%	0.030
2	21.1%	21.4%	0.010	21.1%	21.1%	
3	20.5%	20.3%	0.010	20.5%	20.7%	0.000
4	18.5%	17.8%	0.020	18.5%	17.8%	0.020
Highest 5	17.3%	15.5%	0.050	17.3%	16.5%	0.020
Hypertension	79.2%	84.0%	0.12	79.2%	78.2%	0.020
Diabetes	46.4%	47.9%	0.030	46.4%	47.3%	0.020
History of smoking						
Current	20.2%	19.4%	0.020	20.2%	20.4%	0.000
Former	22.1%	25.8%	0.090	22.1%	23.7%	0.040
Never	57.8%	54.8%	0.060	57.8%	55.9%	0.040
CCS Class						
0	5.0%	4.6%	0.020	5.0%	5.4%	0.020
1	5.8%	6.4%	0.020	5.8%	6.3%	0.020
2	17.0%	14.8%	0.060	17.0%	17.5%	0.010
3	20.1%	18.3%	0.050	20.1%	21.2%	0.030
4	3.8%	5.3%	0.070	3.8%	3.5%	0.010
ACS High Risk	3.3%	6.3%	0.14	3.3%	3.8%	0.020

ACS Intermediate Risk	21.1%	19.7%	0.040	21.1%	18.5%	0.070
ACS Low Risk	23.8%	24.6%	0.020	23.8%	23.9%	0.0010
NY Heart Association						
I	79.3%	65.2%	0.32	79.3%	77.9%	0.030
II	1.1%	2.0%	0.070	1.1%	1.0%	0.010
III	4.9%	6.3%	0.060	4.9%	5.8%	0.040
IV	7.1%	9.0%	0.070	7.1%	7.8%	0.030
Unknown	7.6%	17.5%	0.30	7.6%	7.5%	0.000
Left ventricular function						
20% - 34 %	7.5%	7.8%	0.010	7.5%	8.5%	0.040
35% - 49%	20.4%	20.5%		20.4%	19.8%	0.020
<20%	1.3%	0.9%	0.040	1.3%	1.3%	0.000
>=50%	70.8%	70.7%		70.8%	70.4%	0.010
History of CHF	8.3%	12.4%	0.14	8.3%	9.2%	0.030
History of MI	17.7%	20.5%	0.070	17.7%	17.9%	0.010
Recent MI	35.0%	38.2%	0.070	35.0%	33.2%	0.040
PVD	10.1%	12.4%	0.070	10.1%	11.2%	0.030
CVD	9.0%	10.5%	0.050	9.0%	8.6%	0.010
COPD	8.0%	10.9%	0.10	8.0%	8.2%	0.010
Creatinine Group						0.000
0-120	93.0%	89.3%	0.13	93.0%	92.9%	0.010
121-180	5.6%	6.7%	0.050	5.6%	5.5%	0.000
>180	1.4%	4.0%	0.16	1.4%	1.6%	0.020
Dialysis	0.7%	2.1%	0.12	0.7%	0.8%	0.000
Urgency Status						

Elective	45.2%	38.5%	0.14	45.2%	47.0%	0.040
SemiUrgent	28.5%	32.9%	0.090	28.5%	28.3%	0.010
Urgent	26.3%	28.6%	0.050	26.3%	24.7%	0.040
Extent of coronary artery disease						
DVD with proximal LAD	13.8%	14.8%	0.030	13.8%	13.2%	0.020
DVD without proximal LAD	8.6%	7.7%	0.030	8.6%	8.8%	0.010
LM ± SVD/DVD	16.9%	23.7%	0.17	16.9%	18.2%	0.030
LM with TVD	11.2%	11.9%	0.020	11.2%	10.6%	0.020
TVD without LM	49.5%	41.9%	0.15	49.5%	49.2%	0.010
Off Pump	40.2%	11.2%	0.70	40.2%	37.8%	0.050

ACS, acute coronary syndrome, CCS, Canadian Cardiovascular Society, CHF, congestive heart failure, COPD, chronic obstructive pulmonary disorder, CVD, cerebrovascular disease, DVD, double vessel disease, LAD, left anterior descending artery, LM, left main, MI, myocardial infarction, PVD, peripheral vascular disease, SVD, single vessel disease, TVD, triple vessel disease