JAMA Cardiology | Original Investigation

Long-term Outcomes of Multiple Arterial Coronary Artery Bypass Grafting
A Population-Based Study of Patients in British Columbia, Canada

Aihua Pu, MSc; Lillian Ding, MSc; Jungwon Shin, MSc; Joel Price, MD, MPH; Peter Skarsgard, MD; Daniel R. Wong, MD, MPH; John Bozinovski, MD, MSc; Guy Fradet, MD, MSc; James G. Abel, MD, MSc

IMPORTANCE Although the long-term survival advantage of multiple arterial grafting (MAG) vs the standard use of left internal thoracic artery (LITA) supplemented by saphenous vein grafts (LITA+SVG) has been demonstrated in several observational studies, to our knowledge its safety and other long-term clinical benefits in a large, population-based cohort are unknown.

OBJECTIVE To compare the safety and long-term outcomes of MAG vs LITA+SVG among overall and selected subgroups of patients.

DESIGN, SETTING, AND PARTICIPANTS In this population-based observational study, we included 20 076 adult patients with triple-vessel or left-main disease who underwent primary isolated coronary artery bypass grafting (MAG, n = 5580; LITA+SVG, n = 14 496) in the province of British Columbia, Canada, from January 2000 to December 2014, with follow-up to December 2015. We performed propensity-score analyses by weighting and matching and multivariable Cox regression to minimize treatment selection bias.

EXPOSURES Multiple arterial grafting or LITA+SVG.

MAIN OUTCOMES AND MEASURES Mortality, repeated revascularization, myocardial infarction, heart failure, and stroke.

RESULTS Of 5580 participants who underwent MAG, 586 (11%) were women and the mean (SD) age was 60 (8.7) years. Of 14 496 participants who underwent LITA+SVG, 2803 (19%) were women and the mean (SD) age was 68 (8.9) years. The median (interquartile range) follow-up time was 9.1 (5.1-12.6) years and 8.1 (4.5-11.7) years for the groups receiving MAG and LITA+SVG, respectively. Compared with LITA+SVG, MAG was associated with reduced mortality rates (hazard ratio [HR], 0.79; 95% CI, 0.72-0.87) and repeated revascularization rates (HR, 0.74; 95% CI, 0.66-0.84) in 15-year follow-up and reduced incidences of myocardial infarction (HR, 0.63; 95% CI, 0.47-0.85) and heart failure (HR, 0.79; 95% CI, 0.64-0.98) in 7-year follow-up. The long-term benefits were coherent by all 3 statistical methods and persisted among patient subgroups with diabetes, obesity, moderately impaired ejection fraction, chronic obstructive pulmonary disease, peripheral vascular disease, or renal disease. Multiple arterial grafting was not associated with increased morbidity or mortality rates at 30 days overall or within patient subgroups.

CONCLUSIONS AND RELEVANCE Compared with LITA+SVG, MAG is associated with reduced mortality, repeated revascularization, myocardial infarction, and heart failure among patients with multivessel disease who are undergoing coronary artery bypass grafting without increased mortality or other adverse events at 30 days. The long-term benefits consistently observed across multiple outcomes and subgroups support the consideration of MAG for a broader spectrum of patients who are undergoing coronary artery bypass grafting in routine practice.

JAMA Cardiol. 2017;2(11):1187-1196. doi:10.1001/jamacardio.2017.3705
Published online October 11, 2017.

Supplemental content

Author Affiliations: Cardiac Services BC, Vancouver, British Columbia, Canada (Pu, Ding, Shin); Vancouver General Hospital, Vancouver, British Columbia, Canada (Price, Skarsgard); University of British Columbia, Vancouver, British Columbia, Canada (Price, Skarsgard, Wong, Bozinovski, Fradet, Abel); Royal Columbian Hospital, New Westminster, British Columbia, Canada (Wong); Royal Jubilee Hospital, Victoria, British Columbia, Canada (Bozinovski); Kelowna General Hospital, Kelowna, British Columbia, Canada (Fradet); St. Paul's Hospital, Vancouver, British Columbia, Canada (Abel).

Corresponding Author: James G. Abel, MD, MSc, St. Paul's Hospital, Room 492, 1081 Burrard St, Vancouver, BC V6Z 1Y6, Canada (jabel@providencehealth.bc.ca).

Since the landmark study by Loop et al[1] demonstrated that the use of an internal thoracic artery (ITA) to the left anterior descending artery reduced 10-year mortality and late adverse cardiac events, there has been considerable interest in multiple arterial grafting (MAG) using the right internal thoracic artery (RITA), or a radial artery (RA) in addition to left ITA (LITA) for multivessel coronary artery bypass grafting (CABG).[2-4] Although many observational studies have demonstrated the long-term survival advantages of MAG, the adoption of MAG has been slow because of the absence of randomized clinical trial evidence of long-term benefits[5-8] and observational findings that were limited by single-center study populations,[9-23] noncontemporary surgical cohorts,[9-11,19-21] small sample sizes,[9,10] or an underrepresentation of high-risk patients.[10,18-21] Moreover, conflicting or relatively little information on its safety and other clinical outcomes, such as repeated revascularization, further complicates an evaluation of the "totality of the evidence."[24] A review using the Society of Thoracic Surgeons database reflected a strong reluctance toward using MAG in routine practice,[25] which was limited to fewer than 10% of patients undergoing primary CABG in 2009.

Therefore, a comprehensive evaluation of the effectiveness of MAG in contemporary, routine practice is necessary, particularly in the modern era of evolving surgical techniques, advancing percutaneous coronary intervention (PCI), and improved secondary prevention. In this large, population-based study, we evaluated the safety and long-term outcomes of MAG vs the LITA supplemented by saphenous vein graft (LITA+SVG) overall and among selected subgroups of patients undergoing CABG.

Key Points

Question Does multiple arterial grafting provide long-term clinical benefits without safety concerns among patients who are undergoing coronary artery bypass grafting?

Findings In this population-based study of 20 076 consecutive patients with triple-vessel or left-main disease, multiple arterial grafting was associated with significant reductions in long-term mortality and repeated revascularization without increased perioperative risks. Similar reductions in either mortality or repeated revascularization rates were observed among all subgroups of patients except for those with severely impaired ejection fraction.

Meaning Multiple arterial grafting can be safely extended to a broader spectrum of patients to maximize the long-term benefit of coronary artery bypass grafting among patients with multivessel disease.

Methods

Data Sources

The Cardiac Services British Columbia (BC) registry prospectively captures information on all adult heart surgical procedures, angiographies, angioplasties, and heart rhythm device procedures that are performed in BC. Coronary artery bypass grafting procedures are performed at 5 tertiary care centers. Detailed demographic data, risk factors, procedural details, and postoperative complications are entered prospectively by clinical staff members in each center. All-cause mortality until December 31, 2015, was obtained via linkage to the BC Vital Statistics. Repeated revascularization after index CABG was ascertained from the Cardiac Services BC registry for all patients. Hospitalization information between April 1, 2007, and March 31, 2015, was obtained via linkage to the Discharge Abstract Database (DAD) that contains administrative, clinical, and demographic information on hospital discharges for acute care and day surgery in Canada. This was a retrospective study of data from the Cardiac Services BC registry, and patient information was deidentified. Approval for use of anonymized linked data with a waiver for individual consent was obtained from the University of British Columbia Research Ethics Board.

Study Population and Outcomes

Between January 1, 2000, and December 31, 2014, 24 702 adult patients older than 19 years with triple-vessel or left-main disease underwent isolated CABG in BC. The following groups of patients were excluded: 284 non-BC residents, 3143 patients who did not receive MAG or LITA+SVG (ie, SVG only, isolated LITA, RITA, or RA with SVG), 303 patients who previously underwent open-heart surgery, 616 patients who were undergoing an emergency surgery, 26 patients with prior PCI within 24 hours, and 254 patients with missing baseline covariates. The overall study cohort included 20 076 patients, with 14 496 (72.2%) receiving LITA+SVG and 5580 (27.8%) receiving MAG with or without SVG for the analyses of primary outcomes. Either bilateral internal thoracic arteries with or without RA (RITA-MAG), or LITA with RA (RA-MAG) was used among patients receiving MAG. Of the overall study cohort, 10 545 patients undergoing CABG between April 1, 2007, and December 31, 2014, were linked to the DAD data and constituted the DAD-linked study cohort for the analyses of secondary outcomes.

The primary outcomes were all-cause mortality and repeated revascularization (ie, any subsequent PCI or CABG) following the index CABG. The secondary outcomes were postoperative myocardial infarction, heart failure, stroke, and a combined end point of all previously mentioned outcomes, including all-cause mortality and repeated revascularization. The safety outcomes included 30-day postoperative dialysis, reoperation for bleeding, and sternal reconstruction within 30 and 180 days. Definitions of secondary outcomes are provided in eAppendix 1 in the Supplement.

Statistical Analysis

We evaluated the effect of MAG vs LITA+SVG on clinical outcomes after CABG by applying 3 statistical approaches: 2 propensity score (PS) methods, PS weighting and PS matching, and multivariable Cox regression. All statistical analyses were performed in SAS, version 9.4 (SAS Institute) and R, version 3.2.4 (R Development Core Team) using the R twang package[26] for PS weighting and the SAS macro[27] for PS matching. The level

of significance was defined by a 2-tailed *P* value of <.05 for all statistical tests.

Continuous variables were expressed as mean (SD) and compared using the *t* test. Categorical variables were summarized as proportions and analyzed by the χ^2 test. The cumulative incidences of mortality and the composite end point were estimated by the Kaplan-Meier method. For repeated revascularization and other secondary long-term outcomes, the cumulative incidences were estimated by the cumulative incidence functions, accounting for death as a competing risk. The median duration of follow-up was calculated based on the method of reverse Kaplan-Meier.[28]

All baseline covariates, including the patient demographics, clinical factors and comorbidities in the **Table**, and the surgical year, were incorporated in the calculation of the PS, the probability that a patient receives MAG. In PS matching, the PS was estimated from a non-parsimonious logistic model to form a sample consisting of pairs of MAG and LITA+SVG patients by the nearest-neighbor matching algorithm with a caliper of 0.2 of standard deviations of the logit of the propensity-scores. In PS weighting, patients receiving MAG were assigned a weight of 1 while patients receiving LITA+SVG were assigned a weight equal to the odds of receiving MAG, the PS divided by 1 minus the PS, which was estimated by a generalized boosted model.[29] Adequacy of matching and weighting was confirmed by all baseline covariates having a standardized difference of less than 0.1. The hazard ratios (HRs) for the long-term outcomes were computed from univariable Cox regression models, and the relative risks were estimated for short-term outcomes, with a robust variance estimator to account for the matched or weighted nature of the sample.[30] The HRs for long-term outcomes were also estimated by the multivariable Cox regression models, adjusting for baseline covariates with a *P* value of less than .10 retained in backward elimination. The proportional hazard assumption was confirmed for all Cox regression models. For nonfatal long-term outcomes, patients who died before experiencing these events were censored at the time of death.

We assessed the robustness of the estimated long-term MAG effects to the effect of incomplete revascularization, discharge medications (aspirin, statins, β-blockers, and angiotensin-converting enzyme inhibitor/angiotensin-receptor blockers), and surgeon effect in sensitivity analyses (eAppendix 1 in the Supplement). Although these factors may be prognostic of long-term outcomes, they were not preoperative factors to be included in the propensity-score estimation. Because surgeon effect may be highly correlated with the conduit choice, the adjustment for surgeon effect may lessen or exaggerate the true MAG effect and make interpretation of the estimated MAG effect difficult. Therefore, each of these factors was included as an additional adjustment to the PS weighting analyses to assess the robustness of the results. To address potential residual confounding, we conducted additional PS weighting analyses and tested 3 falsification end points[31] (hip fracture, pneumonia, and urinary tract infection) that were known to be related to patient condition but unlikely to be influenced by the choice of conduit.

We also conducted separate PS weighting analyses to assess MAG benefits among patient subgroups with or without diabetes, 70 years or older, impaired ejection fraction, a high body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 35 or more, peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), and renal disease. To assess whether the magnitude of the MAG effect varied across the relevant subgroups, we tested the significance of the interaction term added to the multivariable Cox regression models based on the overall study cohort.

Results

Multiple arterial grafting use increased from 29% to 36% between 2000 and 2003, declined between 2004 and 2006, and remained around 25% thereafter (eFigure 1 in the Supplement). The median MAG use rate by surgeons was 26.5% (interquartile range [IQR], 12.7%-46.2%).

The group who received MAG consisted of 3056 patients (54.8%) receiving RITA-MAG and 2524 patients (45.2%) receiving RA-MAG. Among patients receiving RITA-MAG, 1239 patients (40.5%) received an RA in addition to bilateral internal thoracic arteries, whereas 1817 patients (59.5%) received bilateral internal thoracic arteries. The demographic and clinical characteristics of the overall study cohort are shown in the Table. Compared with patients who received LITA+SVG, patients receiving MAG were younger, more likely to be male, and less likely to have severely impaired ejection fraction or comorbidities such as renal disease, hypertension, pulmonary hypertension, PVD, COPD, cerebrovascular disease, diabetes, anemia, and arrhythmia.

Perioperative Characteristics

The on-pump rates were comparable between the 2 groups (MAG, 95.4% vs LITA+SVG, 95.7%). For on-pump cases, the mean (SD) pump time was 107.1 minutes (38.6) for the group receiving MAG and 101.2 minutes (32.2) for the group receiving LITA+SVG. The mean (SD) cross-clamp time was 82.5 minutes (29.8) for the group receiving MAG and 79.0 minutes (25.9) for the group receiving LITA+SVG. Single aortic cross-clamp was used among 4142 patients (77.8%) on pump in the MAG group vs 11 263 patients (81.2%) on pump in the LITA+SVG group. The proportion of incomplete revascularization was comparable (MAG, 2.0% vs LITA+SVG, 2.2%), with a mean of number of distal anastomoses of 3.9 in both groups. Conduit details are provided in eAppendix 2 in the Supplement. Both groups had similar discharge prescription rates of aspirin (MAG, 92.1% vs LITA+SVG, 91.0%), β-blockers (MAG, 86.2% vs LITA+SVG, 82.1%), and statins (MAG, 78.3% vs LITA+SVG, 78.1%), but not angiotensin-converting enzyme inhibitor/angiotensin-receptor blockers (MAG, 41.7% vs LITA+SVG, 51.0%).

Unadjusted Outcomes

In the overall study cohort, the median (IQR) follow-up time was 9.1 (5.1-12.6) years and 8.1 (4.5-11.7) years for the groups

Table. Baseline Patient Characteristics of the Overall Study Cohort Before and After PS Weighting

Characteristic	MAG,[a] No. (%) (n = 5580)	LITA+SVG (n = 14 496)		Standardized Difference	
		Before PS Weighting,[a] No. (%)	After PS Weighting,[b] %	Before PS Weighting[c]	After PS Weighting[c]
Age at surgery, mean (SD), y	60.0 (8.7)	68.0 (8.9)	60.3 (8.5)	0.916	0.039
Female sex	586 (10.5)	2803 (19.3)	10.6	0.288	0.004
Ejection fraction, <35%	278 (5.0)	1383 (9.5)	5.1	0.210	0.006
Ejection fraction, 35%-50%	1914 (34.3)	5416 (37.4)	33.4	0.064	0.018
Ejection-fraction, >50%	3388 (60.7)	7697 (53.1)	61.5	0.156	0.015
BMI					
<18.5	10 (0.2)	99 (0.7)	0.2	0.119	0
18.5-29	3785 (67.8)	10001 (69.0)	67.9	0.025	0.001
30-34	1349 (24.2)	3188 (22.0)	24.2	0.051	0.001
>35	436 (7.8)	1208 (8.3)	7.7	0.019	0.003
Urgent status[d]	1549 (27.8)	3385 (23.4)	27.8	0.098	0.002
CCS class IV	2529 (45.3)	6194 (42.7)	44.9	0.052	0.008
NYHA IV	99 (1.8)	304 (2.1)	1.5	0.024	0.019
Left main disease	1785 (32.0)	4331 (29.9)	32.2	0.045	0.004
Previous PCI	948 (17.0)	2629 (18.1)	17.0	0.031	0.001
Prior myocardial infarction	3085 (55.3)	8945 (61.7)	55.2	0.129	0.002
Preoperative arrhythmia	227 (4.1)	1077 (7.4)	4.2	0.170	0.005
History of heart failure	453 (8.1)	2339 (16.1)	8.0	0.294	0.003
Hypertension	4224 (75.7)	12060 (83.2)	76.0	0.175	0.006
Pulmonary hypertension	100 (1.8)	630 (4.3)	1.9	0.192	0.006
PVD	559 (10.0)	2559 (17.7)	10.0	0.254	0.001
COPD	816 (14.6)	3028 (20.9)	14.7	0.177	0.003
Cerebrovascular disease[e]	318 (5.7)	1919 (13.2)	5.7	0.325	0.002
Renal disease, normal[f]	4600 (82.4)	10056 (69.4)	82.4	0.343	0
Renal disease, dysfunction[f]	854 (15.3)	3510 (24.2)	15.3	0.247	0.001
Renal disease, failure without dialysis[f]	90 (1.6)	696 (4.8)	1.6	0.253	0.001
Renal disease, dialysis[f]	36 (0.6)	234 (1.6)	0.7	0.121	0.001
Diabetes	1650 (29.6)	5771 (39.8)	29.5	0.224	0.002
Cancer within 5 y	148 (2.7)	701 (4.8)	2.7	0.136	0.002
Liver disease	378 (6.8)	1272 (8.8)	6.8	0.080	0.003
Moderate/severe anemia[g]	156 (2.8)	1048 (7.2)	2.9	0.269	0.004
Current/recent smoking within 1 mo	988 (17.7)	2013 (13.9)	17.4	0.100	0.007

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CCS class, Canadian Cardiovascular Society Functional Classification of Angina; COPD, chronic obstructive pulmonary disease; LITA+SVG, left internal thoracic artery supplemented by saphenous vein grafts; MAG, multiple arterial grafting; NYHA class, New York Heart Association Class; PCI, percutaneous coronary intervention; PS, propensity score; PVD, peripheral vascular disease.

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10).

[a] Data are expressed as number (%) of patients unless otherwise indicated.

[b] Data are expressed as weighted percentage unless otherwise indicated.

[c] The standardized differences of <0.1 indicate adequate balance of the distribution of baseline risk between the 2 groups.

[d] Urgent status indicates any instances when the patient had left main stenosis greater than 70%, unstable angina receiving nitroglycerin/heparin drip.

[e] Cerebrovascular disease is defined as cerebrovascular accident or transient ischemic attack.

[f] Renal disease is any documented history of renal disease diagnosed including dialysis, acute or chronic renal failure, or estimated glomerular filtration rate less than 60 mL/min/1.73m^2 (by the Cockcroft-Gault formula). Dialysis: patient is currently undergoing either hemodialysis or peritoneal dialysis. Failure without dialysis: acute or chronic renal failure or estimated glomerular filtration rate less than 15 mL/min/1.73m^2 without dialysis. Dysfunction estimated glomerular filtration rate between 15 and 60 mL/min/1.73m^2.

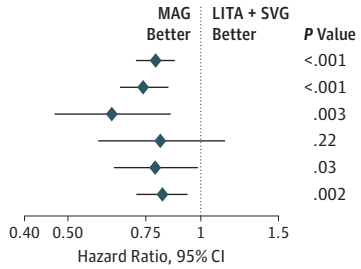
[g] Moderate/severe anemia is defined as hemoglobin level less than 11 g/dL.

receiving MAG and LITA+SVG, respectively. In the DAD-linked study cohort, the median (IQR) follow-up time was 4.2 (2.0-6.2) years and 4.1 (2.1-6.0) years for the groups receiving MAG and LITA+SVG, respectively. Patients receiving MAG had lower incidences of mortality, postoperative dialysis, myocardial infarction, stroke, and heart failure at 30 days (eTable 1 in the Supplement). The group receiving MAG also had lower incidences of mortality and repeated revascularization at 15 years, as well as a lower incidence of myocardial infarction, stroke, heart failure, and the composite end point at 7 years (eFigures 2 and 3 in the Supplement). More than 95% of repeated revascularization was PCI in both groups.

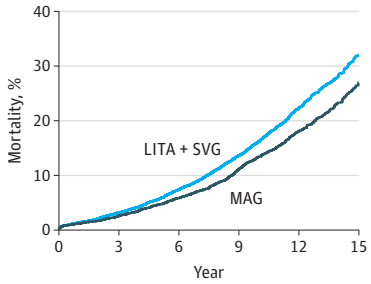
Figure 1. Adjusted Hazard Ratios and Cumulative Incidences of Long-term Outcomes for Multiple Arterial Grafting (MAG) vs Left Internal Thoracic Artery Supplemented by Saphenous Vein Grafts (LITA+SVG)

A Cumulative incidence of long-term outcomes

Long-term Outcome	Cumulative Incidence, (%) LITA + SVG	MAG	Hazard Ratio (95% CI)	P Value
Mortality	32.1	27.0	0.79 (0.72-0.87)	<.001
Repeated revascularization	19.6	14.7	0.74 (0.66-0.84)	<.001
Myocardial infarction	5.9	4.2	0.63 (0.47-0.85)	.003
Stroke	3.2	3.0	0.82 (0.59-1.13)	.22
Heart failure	7.8	6.0	0.79 (0.64-0.98)	.03
Composite end point	23.6	20.0	0.82 (0.72-0.93)	.002



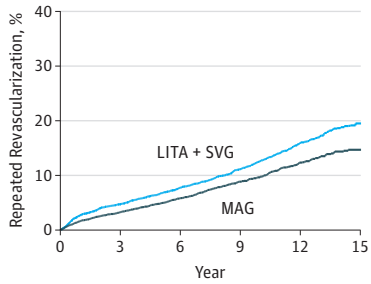
B Mortality rates



No. at risk

LITA + SVG	5351	4495	3460	2341	1223	217
MAG	5580	4695	3635	2494	1360	250

C Repeated revascularization



No. at risk

LITA + SVG	5351	4274	3191	2073	1012	170
MAG	5580	4531	3419	2276	1177	208

A-C, The adjusted cumulative incidences for mortality and repeated revascularization were estimated by incorporating weights that were obtained from propensity score (PS) weighting for the overall study cohort (LITA+SVG, n = 14496; MAG, n = 5580) at the end of 15-year follow-up. The adjusted cumulative incidences for myocardial infarction, stroke, heart failure, and the composite end point were estimated by incorporating weights that were obtained from PS weighting for the Discharge Abstract Database (DAD)-linked study cohort (LITA+SVG, n = 7912; MAG, n = 2633) at the end of 7-year follow-up. Cumulative incidences of mortality and the composite end point were estimated by the Kaplan-Meier method. For nonfatal long-term outcomes, cumulative incidences were estimated by the cumulative incidence function accounting for death as a competing risk. Adjusted hazard ratios were estimated from univariable Cox regression models that incorporated weights that were obtained from PS weighting. *P* values were calculated using the weighted Wald χ^2 test. B and C, The number of patients at risk was calculated by incorporating weights that were obtained from PS weighting (ie, weight of 1 for patients in the group receiving MAG and a weight equal to the odds of receiving MAG for patients in the group receiving LITA+SVG) and rounded to the nearest integer for the group receiving LITA+SVG.

Adjusted Outcomes

Standardized differences less than 0.1 for all covariates in PS weighting (Table) and PS matching indicated balance between the 2 groups (eTable 2 in the Supplement). The results that were obtained from the PS weighting analyses are presented in this section and the results from the PS matching and multivariable Cox regression analyses are provided in eTables 3-9 in the Supplement.

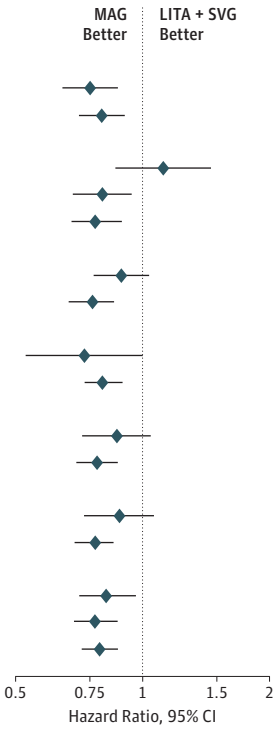
Long-term Outcomes

Compared with LITA+SVG, MAG was associated with a 21% reduction in mortality (hazard ratio [HR], 0.79; 95% CI, 0.72-0.87), and a 26% reduction in repeated revascularization (HR, 0.74; 95% CI, 0.66-0.84) in 15-year follow-up (**Figure 1**). The incidences of myocardial infarction, heart failure, and the composite end point of all long-term outcomes in 7-year follow-up were also significantly lower in the group receiving MAG, whereas the incidence of stroke was comparable in both groups (eFigure 4 in the Supplement).

Multiple arterial grafting was associated with a significantly lower mortality rate regardless of the presence of diabetes, obesity (BMI ≥ 35), or renal disease. Multiple arterial grafting was associated with a significantly lower mortality rate among patients with moderately impaired ejection fraction (35%-50%), but not among patients with a severely impaired ejection fraction of less than 35%. A reduced risk of mortality with MAG, although statistically nonsignificant, was observed in the subgroups who were 70 years or older or had PVD or COPD. The relative mortality reduction that was associated with MAG was significantly smaller in subgroups with an ejection fraction of less than 35%, 70 years or older, or PVD, as indicated by significant *P* values from interaction tests (**Figure 2**). Multiple arterial grafting was associated with a lower repeated revascularization rate in all subgroups except for those with an ejection fraction of less than 35% and those who were 70 years or older (**Figure 3**). Adjusted cumulative incidence curves for mortality and repeated revascularization for each subgroup are provided in eFigures 5-11 in the Supplement.

Figure 2. Adjusted Hazard Ratios of Long-term Mortality for Multiple Arterial Grafting (MAG) vs Left Internal Thoracic Artery Supplemented by Saphenous Vein Grafts (LITA+SVG) in Subgroups

Subgroup	No. of Patients	No. of Patients Undergoing MAG (%)	Hazard Ratio (95% CI)	*P* Value
Diabetes				
Yes	7421	1650 (22.2)	0.75 (0.65-0.87)	.53
No	12655	3930 (31.1)	0.80 (0.71-0.90)	
EF, %				
<35	1661	278 (16.7)	1.12 (0.87-1.45)	.002
35-50	7330	1914 (26.1)	0.77 (0.66-0.90)	
>50	11085	3388 (30.6)	0.77 (0.68-0.89)	
Age, y				
≥70	7636	721 (9.4)	0.89 (0.77-1.03)	.002
<70	12440	4859 (39.1)	0.76 (0.67-0.85)	
BMI				
≥35	1644	436 (26.5)	0.73 (0.53-0.99)	.76
<35	18432	5144 (27.9)	0.80 (0.73-0.89)	
PVD				
Yes	3118	559 (17.9)	0.87 (0.72-1.04)	.02
No	16958	5021 (29.6)	0.78 (0.70-0.87)	
COPD				
Yes	3844	816 (21.2)	0.88 (0.73-1.06)	.05
No	16232	4764 (29.3)	0.77 (0.69-0.85)	
Renal disease				
Yes	5420	980 (18.1)	0.82 (0.71-0.96)	.26
No	14656	4600 (31.4)	0.77 (0.69-0.87)	
Overall	20076	5580 (27.8)	0.79 (0.72-0.87)	



Adjusted hazard ratios were estimated from univariable Cox regression models that incorporated weights that were obtained from propensity score (PS) weighting for each subgroup of the overall study cohort. *P* values were calculated based on the Wald χ^2 test for an interaction term included in a multivariable Cox regression model using the overall study cohort, adjusting for significant baseline covariates with a *P* value of <.1 that was retained in backward elimination. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; EF, ejection fraction; PVD, peripheral vascular disease; Renal disease, dialysis, acute, or chronic renal failure, or estimated glomerular filtration rate of less than 60 L/min/1.73 m^2.

Short-term Outcomes

The incidences of mortality, repeated revascularization, and all safety outcomes were comparable between the 2 groups except for sternal reconstruction within 180 days (**Figure 4**). A further analysis that compared the sternal reconstruction rates between RITA-MAG and RA-MAG demonstrated that the rate was significantly higher among patients who received RITA-MAG than RA-MAG at both 30 days (1.5% vs 0.4%, *P* = .002) and 180 days (2.5% vs 0.6%, *P* < .001). All short-term outcome rates were not significantly higher with MAG compared with LITA+SVG within all high-risk subgroups (eTables 10-16 in the Supplement).

Sensitivity Analyses and Falsification End Point Tests

The magnitude of long-term MAG benefits remained similar after the adjustment for the effect of incomplete revascularization or discharge medications. A further adjustment for surgeon effect did not lessen the MAG benefits in improving long-term survival rates and reducing the incidences of myocardial infarction and heart failure. The advantage of MAG in reducing repeated revascularization rates was moderately attenuated but remained statistically significant (eTable 17 in the Supplement). The falsification tests showed no significant association between the use of MAG and any of the falsification end points (eTable 18 in the Supplement).

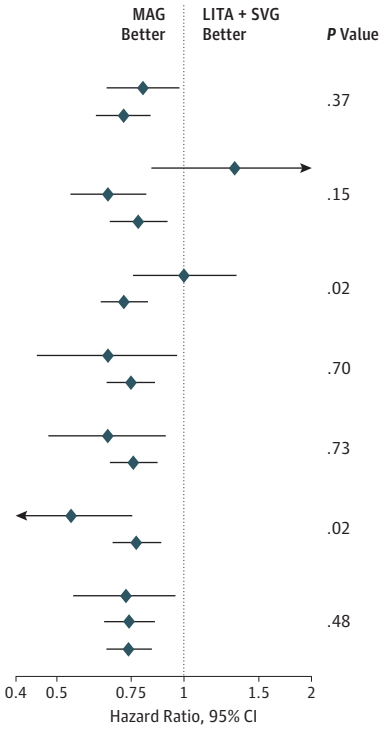
Discussion

Our study is unique in undertaking a comprehensive evaluation of short- and long-term clinical outcomes after CABG in a population-based cohort consisting of 5580 patients who received MAG (27.8%) and 14 496 patients who received LITA+SVG (72.2%). The broad application of MAG using the additional arterial conduit of either the RITA or RA enabled us to evaluate the benefit of MAG in a representative population of patients who were undergoing CABG and address its differential benefits among subgroups. The effect of treatment selection bias and potential confounders in estimating the benefits of MAG was minimized by adjusting for patient demographics, clinical risk factors, comorbidities, and the year of surgery using 3 rigorous statistical adjustment techniques. The long-term MAG benefits in reducing mortality rates and the incidences of repeated revascularization, myocardial infarction, and heart failure were similar across all 3 methods (eTable 9 in the Supplement). The sensitivity analyses demonstrated that the significant long-term benefits of MAG were not qualitatively affected by incomplete revascularization, discharge medications, or surgeon effect. The potential residual confounding was explored by falsification end points.

In 2016, the Arterial Revascularization Trial, a large multicenter randomized clinical trial that compared survival and clinical outcomes between RITA-MAG and single ITA, showed no clinical benefit of RITA-MAG at 5 years.[7] The possible reasons for the midterm findings were discussed by the authors and other investigators.[7,32-34] Despite the absence of randomized clinical trial evidence of long-term clinical benefits of MAG, long-term survival advantages of RITA-MAG over LITA+SVG have been consistently reported in many observational studies[9-11,18-22,35] and

Figure 3. Adjusted Hazard Ratios of Long-term Repeated Revascularization for Multiple Arterial Grafting (MAG) vs Left Internal Thoracic Artery Supplemented by Saphenous Vein Grafts (LITA+SVG) in Subgroups

Subgroup	No. of Patients	No. of Patients Undergoing MAG (%)	Hazard Ratio (95% CI)	*P* Value
Diabetes				
Yes	7421	1650 (22.2)	0.80 (0.66-0.97)	.37
No	12655	3930 (31.1)	0.72 (0.62-0.83)	
EF, %				
<35	1661	278 (16.7)	1.32 (0.84-2.08)	.15
35-50	7330	1914 (26.1)	0.66 (0.54-0.81)	
>50	11085	3388 (30.6)	0.78 (0.67-0.91)	
Age, y				
≥70	7636	721 (9.4)	1.00 (0.76-1.33)	.02
<70	12440	4859 (39.1)	0.72 (0.64-0.82)	
BMI				
≥35	1644	436 (26.5)	0.66 (0.45-0.96)	.70
<35	18432	5144 (27.9)	0.75 (0.66-0.85)	
PVD				
Yes	3118	559 (17.9)	0.66 (0.48-0.90)	.73
No	16958	5021 (29.6)	0.76 (0.67-0.86)	
COPD				
Yes	3844	816 (21.2)	0.54 (0.40-0.75)	.02
No	16232	4764 (29.3)	0.77 (0.68-0.88)	
Renal disease				
Yes	5420	980 (18.1)	0.73 (0.55-0.95)	.48
No	14656	4600 (31.4)	0.74 (0.65-0.85)	
Overall	20076	5580 (27.8)	0.74 (0.66-0.84)	



Adjusted hazard ratios were estimated from univariable Cox regression models that incorporated weights that were obtained from propensity score (PS) weighting for each subgroup of the overall study cohort. *P* values were calculated based on the Wald χ^2 test for an interaction term included in a multivariable Cox regression model using the overall study cohort, adjusting for significant baseline covariates with a *P* value of <.1 that was retained in backward elimination. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; EF, ejection fraction; PVD, peripheral vascular disease; Renal disease, dialysis, acute, or chronic renal failure, or estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2.

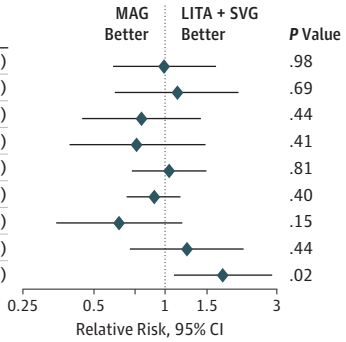
meta-analyses that reported a 19% to 22% mortality reduction.[36-38] Similarly, the survival benefits of RA-MAG were reported in studies from 2 institutions that endorsed liberal RA use.[15-17] A 21% reduction in late mortality was reported by Locker and colleagues[13] in a 15-year study that incorporated both RITA-MAG and RA-MAG. We also observed an equivalent survival benefit of MAG with a more frequent use of RA-MAG, 45.2% in our cohort compared with 14.2% in their study. The consistent survival benefit of MAG observed across these studies, regardless of which second arterial conduit was predominantly used, suggests that both RITA and RA can achieve a similar survival benefit, which is also supported by other recent studies.[34,39,40]

Contrary to the consistent survival benefits of MAG that were shown in observational studies, the effect of MAG on other clinical outcomes has been inconsistent or limited in previous reports. Some studies found reduced incidences of both PCI and CABG individually[19] or as combined repeated revascularization[23] among patients receiving RITA-MAG, whereas the significant benefits of RITA-MAG were limited to reducing subsequent CABG, but not PCI, in other studies.[9,21] Guru et al[41] did not find any significant advantage of MAG over single arterial grafting in reducing repeated revascularization rates, in a mean follow-up of less than 5 years. Little information exists on the effectiveness of RA-MAG on reducing repeated revascularization rates. Although a single-center study found its potential benefits by comparing the frequency of patients returning to the institution for catheterization, the authors acknowledged the underestimation of the actual repeated revascularization need in their study.[16] By contrast, the ascertainment of repeated revascularization from the provincial clinical registry in our study provided a more accurate estimation of the need for repeated revascularization. We observed a 26% reduction in repeated revascularization with MAG compared with LITA+SVG, with the cumulative incidence curves separating early and continuing to diverge to 15 years (Figure 1). Moreover, MAG was also associated with significantly reduced incidences of myocardial infarction and heart failure, consistent with previous studies.[9,19,21,41]

Given the complex decision making in optimizing surgical strategy, identifying the appropriate candidates for MAG is crucial to maximize its long-term benefits.[4,13] Diabetes, obesity, COPD, older age, impaired ejection fraction, PVD, and renal disease have been associated with poor prognoses after CABG and low use of MAG.[3,42] Although studies have consistently reported a long-term MAG survival benefit for patients with diabetes,[35,43-45] findings on repeated revascularization are conflicting.[46,47] We demonstrated a consistent long-term survival benefit and reduced need for repeated revascularization among diabetic patients. Furthermore, we observed a greater absolute mortality rate reduction among patients with diabetes compared with patients without diabetes at 15 years (9.5% vs 3.8%, eFigure 5 in the Supplement). Similarly, MAG was associated with clear long-term advantages in reducing both mortality and repeated revascularization rates among both patients who were and were not obese, which supports existing evidence.[48,49]

Figure 4. Adjusted Relative Risks and Cumulative Incidences of Short-term Outcomes for Multiple Arterial Grafting (MAG) vs Left Internal Thoracic Artery Supplemented by Saphenous Vein Grafts (LITA+SVG)

Short-term Outcome	Cumulative Incidence, %		Relative Risk (95% CI)	*P* Value
	LITA + SVG	MAG		
30-d mortality	0.6	0.6	0.99 (0.61-1.62)	.98
30-d repeat revascularization	0.4	0.4	1.13 (0.62-2.06)	.69
30-d myocardial infarction	1.0	0.8	0.80 (0.45-1.42)	.44
30-d stroke	0.8	0.6	0.76 (0.40-1.47)	.41
30-d heart failure	2.3	2.4	1.04 (0.73-1.49)	.81
30-d reoperation for bleeding	2.2	2.0	0.90 (0.69-1.16)	.40
In-hospital postoperative dialysis	0.5	0.3	0.64 (0.35-1.18)	.15
30-d sternal reconstruction	1.0	1.2	1.24 (0.72-2.13)	.44
180-d sternal reconstruction	1.1	1.9	1.76 (1.10-2.81)	.02



Adjusted cumulative incidences and relative risks for 30-day mortality, 30-day repeated revascularization, 30-day reoperation for bleeding, and in-hospital postoperative dialysis were estimated by incorporating weights that were obtained from propensity score (PS) weighting from the overall study cohort (LITA+SVG, n = 14496; MAG, n = 5580). Adjusted cumulative incidences and relative risks for 30-day myocardial infarction, stroke, and heart failure were estimated incorporating weights obtained from PS weighting from the Discharge Abstract Database (DAD)-linked study cohort (LITA+SVG, n = 7912; MAG, n = 2633). Adjusted cumulative incidences and relative risks for 30-day and 180-day sternal reconstruction were estimated by incorporating weights that were obtained from PS weighting from a subset of patients in the DAD-linked study cohort who were undergoing CABG from April 1, 2007, to September 30, 2014 (LITA+SVG, n = 7614; MAG, n = 2544). Adjusted relative risks and *P* values from the χ^2 tests were calculated by incorporating weights that were obtained from PS weighting.

To our knowledge, no recent studies have examined the long-term effect of MAG among patients with renal disease, COPD, or PVD. The MAG benefits in reducing both mortality and repeated revascularization rates were consistent regardless of the presence of renal disease. A greater reduction in repeated revascularization rates and a reduced survival benefit were observed among patients with COPD or PVD. Compared with younger patients, the survival benefit among elderly patients was significantly reduced in our study; however, an 11% reduction in mortality of borderline statistical significance supports the MAG benefits that were reported in 3 studies[50-52] but conflicts with other studies.[40,53,54] The current evidence of MAG benefits is robust for patients with moderately impaired ejection fraction[19,20,42,55] but conflicting for patients with severely impaired ejection fraction. Our finding of no survival benefit for patients with an ejection fraction of less than 35% is consistent with those 2 RITA-MAG studies[42,56] but differs from 1 RA-MAG study.[55]

Lytle et al[20] suggested that heterogeneous mortality risks across patient spectrums were the underlying mechanism for differential MAG effects. Superior long-term patency of the second arterial conduit may translate into improved clinical outcomes, but its influence must be strong enough to offset the influences of risk factors that limit survival after CABG.[20,57] Therefore, a loss of MAG benefits among patients with severely impaired ejection fraction is likely related to the influence of severe left ventricular dysfunction and other noncardiac comorbidities on survival, as discussed in other studies.[42,56] Analogously, a moderated benefit of MAG among elderly patients supports this inference because of diminished life expectancy and more comorbidities.[40,53] Nevertheless, a survival benefit greater than 10% was observed for most of the subgroups, demonstrating that a potential MAG benefit can be realizable, even among high-risk patient subgroups.

Perceived concerns regarding increased perioperative mortality and morbidity, particularly sternal wound complications associated with RITA-MAG, have limited its use to a small proportion of patients undergoing CABG.[36] We observed similar incidences of adverse events at 30 days for the groups receiving MAG and LITA+SVG but a significantly higher risk of sternal reconstruction at 180 days in the group receiving MAG, although the absolute increase was small (MAG, 1.9% vs LITA+SVG, 1.1%; $P = .02$). Our findings are consistent with those of the Arterial Revascularization Trial that reported similar 30-day adverse outcomes between the 2 groups and a higher incidence of sternal reconstruction associated with RITA-MAG at 6 weeks from randomization (RITA-MAG, 1.9% vs single ITA, 0.6%).[6] Furthermore, we confirmed that RA-MAG was associated with a significantly lower risk of sternal reconstruction than RITA-MAG at 180 days (0.6% vs 2.5%, $P < .001$), which corroborated findings from another study.[58] Among all high-risk subgroups, MAG was not associated with significantly higher incidences of 30-day adverse events. Nevertheless, a higher likelihood of sternal reconstruction at 180 days with MAG, although statistically nonsignificant, among elderly patients or patients with diabetes, PVD, or obesity suggests a need for incorporating strategies to mitigate sternal wound complications in considering MAG for these patients (eTables 12-18 in the Supplement).

Limitations

Our results should be interpreted in the context of the inherent limitations of observational studies. We attempted to minimize treatment selection bias by using rigorous statistical adjustment techniques; however, there remains the possibility of potential bias because of unmeasured confounders. The choice of a specific revascularization strategy for a patient is often subjective and may be affected

by factors that are prognostically important but unavailable in the data. Subtle factors, such as the size and quality of coronary targets and patient frailty, are unmeasured but important for a surgeon's choice of revascularization strategy and may influence clinical outcomes.[36,59] Nevertheless, the absence of an association between MAG and the falsification end points suggests that patients who received MAG were not systematically healthier after adjustment. Therefore, the observed MAG benefit is less likely to be owing to residual confounding.

Conclusions

Compared with LITA+SVG, MAG is associated with reduced incidences of mortality, repeated revascularization, myocardial infarction, and heart failure among patients with multivessel disease who are undergoing CABG without increased incidences of mortality or other adverse events at 30 days. The long-term benefits consistently observed across multiple outcomes and subgroups support the consideration of MAG for a broader spectrum of patients.

ARTICLE INFORMATION

Accepted for Publication: August 24, 2017.

Published Online: October 11, 2017. doi:10.1001/jamacardio.2017.3705

Author Contributions: Ms Pu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Pu, Ding, Price, Bozinovski, Fradet, Abel.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Pu, Ding, Shin, Price, Abel.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Pu, Ding, Shin, Price, Fradet, Abel.
Administrative, technical, or material support: Ding, Price, Fradet, Abel.
Supervision: Ding, Price, Wong, Fradet, Abel.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This study was supported by Cardiac Services, British Columbia.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; analysis and interpretation of the data; or preparation of the manuscript.

Additional Information: The analytic work for this study was performed at the Cardiac Services, British Columbia.

REFERENCES

1. Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *N Engl J Med*. 1986;314(1):1-6.

2. Gaudino M, Taggart D, Suma H, Puskas JD, Crea F, Massetti M. The choice of conduits in coronary artery bypass surgery. *J Am Coll Cardiol*. 2015;66(15):1729-1737.

3. Taggart DP. Current status of arterial grafts for coronary artery bypass grafting. *Ann Cardiothorac Surg*. 2013;2(4):427-430.

4. Kurlansky P. Multiple arterial grafting for coronary revascularization: "a guide for the perplexed". *Trends Cardiovasc Med*. 2016;26(7):616-623.

5. Taggart DP, Lees B, Gray A, Altman DG, Flather M, Channon K; ART Investigators. Protocol for the Arterial Revascularisation Trial (ART). a randomised trial to compare survival following bilateral versus single internal mammary grafting in coronary revascularisation [ISRCTN46552265]. *Trials*. 2006;7:7.

6. Taggart DP, Altman DG, Gray AM, et al; ART Investigators. Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). *Eur Heart J*. 2010;31(20):2470-2481.

7. Taggart DP, Altman DG, Gray AM, et al; ART Investigators. Randomized trial of bilateral versus single internal-thoracic-artery grafts. *N Engl J Med*. 2016;375(26):2540-2549.

8. Yanagawa B, Verma S, Puskas JD. Bilateral internal thoracic arteries: what is the state of the ART? *Curr Opin Cardiol*. 2017;32(5):594-599.

9. Rankin JS, Tuttle RH, Wechsler AS, Teichmann TL, Glower DD, Califf RM. Techniques and benefits of multiple internal mammary artery bypass at 20 years of follow-up. *Ann Thorac Surg*. 2007;83(3):1008-1014.

10. Glineur D, D'hoore W, Price J, et al. Survival benefit of multiple arterial grafting in a 25-year single-institutional experience: the importance of the third arterial graft. *Eur J Cardiothorac Surg*. 2012;42(2):284-290.

11. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. *Ann Thorac Surg*. 2010;90(1):101-108.

12. Kelly R, Buth KJ, Légaré JF. Bilateral internal thoracic artery grafting is superior to other forms of multiple arterial grafting in providing survival benefit after coronary bypass surgery. *J Thorac Cardiovasc Surg*. 2012;144(6):1408-1415.

13. Locker C, Schaff HV, Dearani JA, et al. Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease. *Circulation*. 2012;126(9):1023-1030.

14. Parsa CJ, Shaw LK, Rankin JS, et al. Twenty-five-year outcomes after multiple internal thoracic artery bypass. *J Thorac Cardiovasc Surg*. 2013;145(4):970-975.

15. Tranbaugh RF, Dimitrova KR, Friedmann P, et al. Radial artery conduits improve long-term survival after coronary artery bypass grafting. *Ann Thorac Surg*. 2010;90(4):1165-1172.

16. Tranbaugh RF, Dimitrova KR, Friedmann P, et al. Coronary artery bypass grafting using the radial artery: clinical outcomes, patency, and need for reintervention. *Circulation*. 2012;126(11)(suppl 1):S170-S175.

17. Zacharias A, Habib RH, Schwann TA, Riordan CJ, Durham SJ, Shah A. Improved survival with radial artery versus vein conduits in coronary bypass surgery with left internal thoracic artery to left anterior descending artery grafting. *Circulation*. 2004;109(12):1489-1496.

18. Mohammadi S, Dagenais F, Doyle D, et al. Age cut-off for the loss of benefit from bilateral internal thoracic artery grafting. *Eur J Cardiothorac Surg*. 2008;33(6):977-982.

19. Lytle BW, Blackstone EH, Loop FD, et al. Two internal thoracic artery grafts are better than one. *J Thorac Cardiovasc Surg*. 1999;117(5):855-872.

20. Lytle BW, Blackstone EH, Sabik JF, Houghtaling P, Loop FD, Cosgrove DM. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. *Ann Thorac Surg*. 2004;78(6):2005-2012.

21. Stevens LM, Carrier M, Perrault LP, et al. Single versus bilateral internal thoracic artery grafts with concomitant saphenous vein grafts for multivessel coronary artery bypass grafting: effects on mortality and event-free survival. *J Thorac Cardiovasc Surg*. 2004;127(5):1408-1415.

22. Grau JB, Ferrari G, Mak AW, et al. Propensity matched analysis of bilateral internal mammary artery versus single left internal mammary artery grafting at 17-year follow-up: validation of a contemporary surgical experience. *Eur J Cardiothorac Surg*. 2012;41(4):770-775.

23. Benedetto U, Amrani M, Gaer J, et al; Harefield Cardiac Outcomes Research Group. The influence of bilateral internal mammary arteries on short- and long-term outcomes: a propensity score matching in accordance with current recommendations. *J Thorac Cardiovasc Surg*. 2014;148(6):2699-2705.

24. Pocock SJ, Stone GW. The primary outcome is positive: is that good enough? *N Engl J Med*. 2016;375(10):971-979.

25. ElBardissi AW, Aranki SF, Sheng S, O'Brien SM, Greenberg CC, Gammie JS. Trends in isolated coronary artery bypass grafting: an analysis of the Society of Thoracic Surgeons adult cardiac surgery database. *J Thorac Cardiovasc Surg*. 2012;143(2):273-281.

26. Griffin BA, Ridgeway G, Morral AR, et al. *Toolkit for Weighting and Analysis of Nonequivalent Groups (TWANG) Website*. Santa Monica, CA: RAND Corporation; 2014.

27. Coca-Perraillon M. Local and global optimal propensity score matching. Paper presented at: SAS Global Forum 2007; April 2-5, 2017; Orlando, FL. http://www2.sas.com/proceedings/forum2007/185-2007.pdf. Accessed February 13, 2016.

28. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17(4):343-346.

29. McCaffrey DF, Ridgeway G, Morral AR. Propensity score estimation with boosted regression for evaluating causal effects in observational studies. *Psychol Methods*. 2004;9(4):403-425.

30. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med*. 2014;33(7):1242-1258.

31. Prasad V, Jena AB. Prespecified falsification end points: can they validate true observational associations? *JAMA*. 2013;309(3):241-242.

32. Gaudino M, Tranbaugh R, Fremes S. Bilateral versus single internal-thoracic-artery grafts. *N Engl J Med*. 2017;376(18):e37.

33. Raza S, Blackstone EH, Sabik JF III. Bilateral versus single internal-thoracic-artery grafts. *N Engl J Med*. 2017;376(18):e37.

34. Taggart DP, Altman DG, Flather M, et al; ART (Arterial Revascularization Trial) Investigators. Associations between adding a radial artery graft to single and bilateral internal thoracic artery grafts and outcomes: insights from the Arterial Revascularization Trial. *Circulation*. 2017;136(5):454-463.

35. Puskas JD, Sadiq A, Vassiliades TA, Kilgo PD, Lattouf OM. Bilateral internal thoracic artery grafting is associated with significantly improved long-term survival, even among diabetic patients. *Ann Thorac Surg*. 2012;94(3):710-715.

36. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet*. 2001;358(9285):870-875.

37. Weiss AJ, Zhao S, Tian DH, Taggart DP, Yan TD. A meta-analysis comparing bilateral internal mammary artery with left internal mammary artery for coronary artery bypass grafting. *Ann Cardiothorac Surg*. 2013;2(4):390-400.

38. Yi G, Shine B, Rehman SM, Altman DG, Taggart DP. Effect of bilateral internal mammary artery grafts on long-term survival: a meta-analysis approach. *Circulation*. 2014;130(7):539-545.

39. Schwann TA, Hashim SW, Badour S, et al. Equipoise between radial artery and right internal thoracic artery as the second arterial conduit in left internal thoracic artery-based coronary artery bypass graft surgery: a multi-institutional study. *Eur J Cardiothorac Surg*. 2016;49(1):188-195.

40. Tranbaugh RF, Schwann TA, Swistel DG, et al. Coronary artery bypass graft surgery using the radial artery, right internal thoracic artery, or saphenous vein as the second conduit. *Ann Thorac Surg*. 2017;104(2):553-559.

41. Guru V, Fremes SE, Tu JV. How many arterial grafts are enough? a population-based study of midterm outcomes. *J Thorac Cardiovasc Surg*. 2006;131(5):1021-1028.

42. Galbut DL, Kurlansky PA, Traad EA, Dorman MJ, Zucker M, Ebra G. Bilateral internal thoracic artery grafting improves long-term survival in patients with reduced ejection fraction: a propensity-matched study with 30-year follow-up. *J Thorac Cardiovasc Surg*. 2012;143(4):844-853.e4.

43. Hoffman DM, Dimitrova KR, Decastro H, et al. Improving long term outcome for diabetic patients undergoing surgical revascularization by use of the radial artery conduit: a propensity matched study. *J Cardiothorac Surg*. 2013;8(1):27.

44. Dorman MJ, Kurlansky PA, Traad EA, Galbut DL, Zucker M, Ebra G. Bilateral internal mammary artery grafting enhances survival in diabetic patients: a 30-year follow-up of propensity score-matched cohorts. *Circulation*. 2012;126(25):2935-2942.

45. Schwann TA, Al-Shaar L, Engoren M, Habib RH. Late effects of radial artery vs saphenous vein grafting for multivessel coronary bypass surgery in diabetics: a propensity-matched analysis. *Eur J Cardiothorac Surg*. 2013;44(4):701-710.

46. Calafiore AM, Di Mauro M, Di Giammarco G, et al. Single versus bilateral internal mammary artery for isolated first myocardial revascularization in multivessel disease: long-term clinical results in medically treated diabetic patients. *Ann Thorac Surg*. 2005;80(3):888-895.

47. Stevens LM, Carrier M, Perrault LP, et al. Influence of diabetes and bilateral internal thoracic artery grafts on long-term outcome for multivessel coronary artery bypass grafting. *Eur J Cardiothorac Surg*. 2005;27(2):281-288.

48. Benedetto U, Montecalvo A, Kattach H, Amrani M, Raja SG; Harefield Cardiac Outcomes Research Group. Impact of the second internal thoracic artery on short- and long-term outcomes in obese patients: a propensity score matched analysis. *J Thorac Cardiovasc Surg*. 2015;149(3):841-7.e1, 2.

49. Vitulli P, Frati G, Benedetto U. Bilateral internal mammary artery grafting in obese: outcomes, concerns and controversies. *Int J Surg*. 2015;16(Pt B):158-162.

50. Habib RH, Schwann TA, Engoren M. Late effects of radial artery versus saphenous vein grafting in patients aged 70 years or older. *Ann Thorac Surg*. 2012;94(5):1478-1484.

51. Pettinari M, Sergeant P, Meuris B. Bilateral internal thoracic artery grafting increases long-term survival in elderly patients. *Eur J Cardiothorac Surg*. 2015;47(4):703-709.

52. Shi WY, Hayward PA, Fuller JA, et al. Is the radial artery associated with improved survival in older patients undergoing coronary artery bypass grafting? an analysis of a multicentre experience. *Eur J Cardiothorac Surg*. 2016;49(1):196-202.

53. Benedetto U, Amrani M, Raja SG; Harefield Cardiac Outcomes Research Group. Guidance for the use of bilateral internal thoracic arteries according to survival benefit across age groups. *J Thorac Cardiovasc Surg*. 2014;148(6):2706-2711.

54. Kieser TM, Lewin AM, Graham MM, et al; APPROACH Investigators. Outcomes associated with bilateral internal thoracic artery grafting: the importance of age. *Ann Thorac Surg*. 2011;92(4):1269-1275.

55. Schwann TA, Al-Shaar L, Tranbaugh RF, et al. Multi versus single arterial coronary bypass graft surgery across the ejection fraction spectrum. *Ann Thorac Surg*. 2015;100(3):810-817.

56. Mohammadi S, Kalavrouziotis D, Cresce G, et al. Bilateral internal thoracic artery use in patients with low ejection fraction: is there any additional long-term benefit? *Eur J Cardiothorac Surg*. 2014;46(3):425-431.

57. Schwann TA, Tranbaugh RF, Dimitrova KR, et al. Time-varying survival benefit of radial artery versus vein grafting: a multiinstitutional analysis. *Ann Thorac Surg*. 2014;97(4):1328-1334.

58. Tranbaugh RF, Dimitrova KR, Lucido DJ, et al. The second best arterial graft: a propensity analysis of the radial artery versus the free right internal thoracic artery to bypass the circumflex coronary artery. *J Thorac Cardiovasc Surg*. 2014;147(1):133-140.

59. Buxton BF, Shi WY, Tatoulis J, Fuller JA, Rosalion A, Hayward PA. Total arterial revascularization with internal thoracic and radial artery grafts in triple-vessel coronary artery disease is associated with improved survival. *J Thorac Cardiovasc Surg*. 2014;148(4):1238-1243.