Effect of total arterial grafting in the Arterial Revascularization Trial

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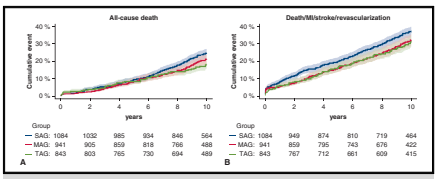
ABSTRACT

Objectives: The Arterial Revascularization Trial (ART) was designed to compare 10-year survival in bilateral versus single internal thoracic artery grafts. The intention-to-treat analysis has showed comparable outcomes between the 2 groups but an explanatory analysis suggested that those receiving 2 or more arterial grafts had better survival. Whether the exclusive use of arterial grafts provide further benefit is unclear.

Methods: We performed an exploratory analysis of the ART based on conduits actually received (as-treated principle). From ART cohort, only patients receiving at least 3 grafts were included. The final population consisted of 1084, 1010, and 390 patients in the single arterial graft (SAG) group, in the multiple arterial graft (MAG) group (2 or more arterial grafts with additional saphenous veins) and total arterial graft (TAG) group (3 or more arterial grafts only) respectively. Inverse probability of treatment weighting was used for comparison.

Results: When compared with the SAG group, there was a significant trend toward a reduction of 10-year mortality in the MAG and TAG group (test for trend $P = .02$). The TAG group was associated with the lowest risk of late mortality (hazard ratio, 0.68; 95% confidence interval, 0.48-0.96; $P = .03$) and with a significant risk reduction of the composite of death/myocardial infarction/stroke and repeat revascularization (hazard ratio, 0.71; 95% confidence interval, 0.53-0.94; $P = .02$).

Conclusions: When compared with SAG, both MAG and TAG represent valuable strategies to improve clinical outcomes following coronary artery bypass grafting but TAG can potentially provide further benefit. (J Thorac Cardiovasc Surg 2020;■:1-8)



A, 10-year mortality and B, incidence of death/MI/stroke/repeat revascularization.

CENTRAL MESSAGE

Multiple and total arterial grafting are valuable strategies to improve clinical outcomes following coronary artery bypass; total arterial grafting can potentially provide further benefit.

PERSPECTIVE

Our findings support the hypothesis that both multiple and total arterial grafting represent valuable strategies to improve clinical outcomes following coronary artery bypass surgery but total arterial grafting can potentially provide further benefit in a selected low-risk population. Further studies are necessary to provide final evidence.

See Commentary on page XXX.

ADULT

Graft failure after coronary artery bypass grafting (CABG) causes recurrent angina, need for repeat intervention, and poorer survival.[1] Arterial grafts, including bilateral internal thoracic artery (BITA) grafts and/or the radial artery, have been consistently shown to provide superior angiographic patency rates when compared with saphenous vein grafts (SVGs),[2,3] and the exclusive use of arterial grafts (total arterial grafting [TAG]) has also been advocated as the best revascularization strategy.[4-9] However, TAG is still largely underused to supplement a single arterial graft (SAG) and multiple arterial graft (MAG) strategies.

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Abbreviations and Acronyms

ART = Arterial revascularization trial
BITA = bilateral internal thoracic arteries
CABG = coronary artery bypass grafting
CI = confidence interval
HR = hazard ratio
IPTW = inverse probability of treatment weighting
MAG = multiple arterial graft
MI = myocardial infarction
PS = propensity score
SAG = single arterial graft
SITA = single internal thoracic artery
SVG = saphenous vein graft
TAG = total arterial graft

Scanning this QR code will take you to the article title page to access supplementary information.

The Arterial Revascularization Trial (ART) was designed to compare 10 years' survival in bilateral (BITA) versus single internal thoracic artery (SITA) grafts. The intention-to-treat analysis has shown comparable outcomes between the 2 groups.[10] However, SVG was used in 60% of BITA grafts, and this may have partially contributed to the equipoise observed in the intention-to-treat analysis.

Hence, we aimed to investigate the potential advantage of TAG versus MAG with additional SVG over SAG strategy by performing an exploratory analysis of the ART based on conduits actually received (as treated).

METHODS

This research adheres to the principles set forth in the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html). For the purpose of the present post-hoc analysis, patients from the ART (n = 3102) were classified according to an as-treated principle depending on number of SVG and arterial grafts actually received. Patients receiving an SAG plus SVG were included in the SAG group; patients receiving 2 or more arterial grafts with additional SVG were included in the MAG group; patients receiving arterial grafts only included in the TAG group. The primary endpoint was 10-year survival. Inverse probability of treatment weighting (IPTW) was used for comparison. In the present analysis, we included only those patients who received 3 or more grafts. Patients with no information on whether supplemental conduits were radial artery or vein (n = 25), those who received 1 graft only (n = 20), those not receiving at least 1 internal thoracic artery (n = 35), or those where multiple arterial grafting was achieved exclusively using sequential SITA graft (n = 85) were excluded.

Trial Design

The ART was approved by the institutional review board of all participating centers, and informed consent was obtained from each participant. The protocol for the ART has been published.[11] To summarize, the ART is a 2-arm, randomized multicenter trial conducted in 28 hospitals in 7 countries, with patients being randomized equally to SITA or BITA grafts. Eligible patients were those with multivessel coronary artery disease involving at least the left anterior descending artery and the circumflex artery undergoing CABG, including urgent patients. Only emergency patients (refractory myocardial ischemia [MI]/cardiogenic shock) and those requiring single grafts or redo CABG were excluded.

Follow-up

Questionnaires were sent to study participants by mail every year after surgery. No clinic visits were planned apart from the routine clinical 6-week postoperative visit. Participants were sent stamped addressed envelopes to improve the return rates of postal questionnaires. Study coordinators contacted participants by telephone to alert them to the questionnaire's arrival and to ask them about medications, adverse events, and health services resource use.

Study Outcomes

For the present analysis, the primary outcome was 10-year mortality and the composite of death, MI, stroke, and/or repeat revascularization.

Definitions

ART definitions were used for the present analysis. The burden of native coronary artery disease was assessed by reporting the following 3 characteristics for each graft performed: quality of the target (1-3; 1 = good, 2 = moderate, 3 = poor), vessel diameter assessed by means of intraoperative probes, and the need for endarterectomy.

Death was classified into cardiovascular and noncardiovascular causes, where possible, using autopsy reports and death certificates. Congestive heart failure, arrhythmia or MI, pulmonary embolus, and dissection were considered cardiovascular causes of death. Because pulmonary embolus and dissection are not directly related to the conduits used, in the present analysis we considered all-cause death only. MI was diagnosed when 2 of the following 3 criteria were present: (1) unequivocal electrocardiography changes; (2) elevation of cardiac enzyme(s) above twice the upper limit of normal or diagnostic troponin rises; (3) chest pain typical for acute MI that lasted more than 20 minutes. Stroke was defined as new neurologic deficit evidenced by clinical signs of paresis, paraplegia, or new cognitive dysfunction, including any mental status alteration lasting more than 24 hours, and/or evidence on computed tomography or magnetic resonance imaging scan of recent brain infarct (less than 6 months). Repeat revascularization was defined as coronary bypass surgery or percutaneous coronary intervention performed after the initial trial procedure.

Statistical Analysis

Continuous variables were reported as mean and standard deviation, and categorical variables were reported as count and percentage. The rate of missing data was less than 1% for all variables included in the propensity score (PS) model. The mean and the most frequent value were used to impute continuous and categorical variables, respectively. To compare the 3 groups, IPTW was used and the treatment effect on the treated was estimated to draw inferences about the relative effectiveness of the 3 treatment groups. For this purpose, a generalized boosted model was implemented to estimate PS adjusting for pretreatment covariates, age, female sex, diabetes, chronic obstructive pulmonary disease, asthma, creatinine, left ventricular ejection fraction, peripheral vascular disease, preoperative atrial fibrillation, MI, right coronary artery disease, off-pump status, race, New York Heart Association functional class, hypertension, hyperlipemia, and cerebrovascular disease. The PS was assumed as the probability that an individual with pretreatment characteristics X receives SAG (twang R package). We gave each treatment case a weight of 1 and each comparison case a weight wi = p(xi)/(1 − p[xi]). The absolute standardized mean

difference was used as a balance metric to summarize the difference between 2 univariate distributions of a single pretreatment variable. A value ≥0.10 was considered as an indicator of imbalance. The treatment effect estimates on primary endpoints were obtained by using a doubly robust estimation, which combines a form of outcome regression (multivariate proportional hazard model) with a model for the exposure (ie, IPTW). SAG was used as reference in all comparisons. A combination of IPTW and covariate adjustment corrects for residual imbalance after weighting. Moreover, treatment effect estimators that use an outcomes regression model and PS are "doubly robust" in the sense that if either the PS model is correct or the regression model is correct then the treatment effect estimator will be unbiased.

Treatment effect was reported as hazard ratio (HR) and 95% confidence interval (95% CI). Subdistribution HR were calculated for nonfatal endpoints (MI, stroke, repeat revascularization). Doubly robust adjustment was also used for test for trend analysis to investigate whether the hypothesis of an incremental benefit from MAG over SAG and from TAG over SAG. Surgeon ID was included as a stratifying variable to account for surgeon related clustering effect. Treatment effect was also estimated after restricting analysis to patients older than 70 years and with insulin-dependent diabetes. For sensitivity analysis, we pooled TAG and MAG strategies in a single group (MAG/TAG group) and compared with a SAG using multivariable Cox regression model. For completeness, unadjusted comparisons were estimated forcing the treatment variable only in the regression model.

For each patient, we also calculated the TAG index according to the following formula:

$$TAG\ index = \frac{Number\ of\ Arterial\ Grafts}{Number\ of\ Total\ Grafts}$$

The TAG index is an intuitive index of the proportion of revascularization achieved with arterial grafts. TAG index = 1 correspond to arterial grafts only (TAG), whereas TAG index = 0 corresponds to revascularization with SVG only. By forcing the TAG index (as a continuous and categorial variable as <1/3; 1/3 to 2/3; >2/3) into a multivariable Cox model stratified by number of total grafts, we tested the hypothesis of a significant relationship between the proportion of arterial revascularization and a reduction of 10 year-adverse events. The relationship between different values of TAG index and risk of adverse events was reported as HR and 95% CI using the median value of TAG index as reference.

As sensitivity analysis, treatment effect was tested in a multivariable Cox regression analysis stratified by number of grafts.

All statistical analysis was performed using R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The final population consisted of 1084, 1010, and 390 patients in the SAG, MAG, and TAG group, respectively. Only 139 (5.6%) patients did not complete the 10-year follow-up, 59 (5.4%) in the SAG, 56 (5.5%) in the MAG, and 24 (6.1) in the TAG group. The mean follow-up in this group was 5.2 years. The graft configuration used in each group is summarized in Table E1. The 3 groups presented some differences in baseline characteristics (Table 1, average standardized mean difference >0.10). In particular, patients in the TAG group were 2 years younger on average and were less likely to have a concomitant right coronary artery disease, a worse New York Heart Association functional class, but more likely to have an left ventricular ejection fraction <50%. Guideline-directed medical therapy at 10 years is shown in Table E2. PS weighting created 3 groups comparable for all baseline characteristics (Table 2, Figure 1, Table E3, and Figure E1). The distinction between cardiovascular and noncardiovascular causes of death is presented in Table E4, and Table E5 shows the incidence of sternal wound infection requiring reconstruction.

10 year-outcome analysis is reported in Table 3. In the PS-weighted sample, we observed a significant trend toward a reduction of 10-year mortality across the 3 groups (test for trend = 0.02; Figure 2, *A*) and TAG was associated with a significant risk reduction of all-cause death when compared with SAG (HR, 0.68; 95% CI, 0.48-0.96; $P = .03$). The same trend was observed for the revascularization ($P = .04$) and the composite of death/MI/stroke and repeat revascularization ($P = .01$), with TAG being associated with a significant risk reduction of the composite of death/MI/stroke and repeat revascularization (0.71; 95% CI, 0.53-0.94; $P = .02$; Figure 2, *B*) when compared with SAG.

The results of analysis in patients older than 70 years old and insulin-dependent diabetic patients are depicted in Tables E6 and E7. TAG was associated with a lower incidence of mortality, and both MAG and TAG with lower incidence of the composite of mortality, MI, stroke, and/or revascularization in patients with insulin-dependent diabetes. Multivariable Cox models (Table E8) confirmed that when compared with SAG, TAG was associated with a significant risk reduction of 10-year mortality and that MAG and TAG were associated with a significant risk reduction of the composite of death, MI, stroke, and repeat revascularization.

When TAG and MAG strategies were pooled together in a single group (MAG/TAG group), they were superior to SAG in terms of 10-year mortality and incidence of MACCE (Table E9). Table E10 depicts the unadjusted treatment effect estimation.

Finally, we observed a significant linear relationship between the TAG index and the risk of 10-year mortality (HR, 0.68; 95% CI, 0.47-0.97; $P = .03$) and composite outcome (HR, 0.68; 95% CI, 0.51-0.90; $P = .007$, Figure 3, *A* and *B*; Table 4). When the TAG index was used as categorial variable, when compared with cases with TAG index < 1/3, a larger proportion of arterial revascularization (TAG index between 1/3 and 2/3 or TAG index > 2/3) was associated with a significantly lower risk of 10-year mortality and composite of death/MI/stroke and repeat revascularization.

DISCUSSION

The main finding of the present post-hoc analysis of the ART was that we observed an incremental benefit in moving from SAG to MAG and TAG in terms of reduction of 10-year mortality and the composite of death/MI/stroke and repeat revascularization. When compared with SAG, the MAG group showed a numerically lower rate of 10-year

TABLE 1. Patients characteristics in the original sample

	SAG	MAG	TAG	*P* value	SMD
n	1084	1010	390		
Age, y	64.20 (8.92)	63.42 (8.86)	62.03 (8.95)	<.001	0.162
Nonwhite	93 (8.6)	91 (9.0)	24 (6.2)	.213	0.072
Female sex	145 (13.4)	118 (11.7)	57 (14.6)	.276	0.058
NYHA functional class 3-4	224 (20.7)	237 (23.5)	60 (15.4)	.004	0.137
Diabetes	253 (23.3)	237 (23.5)	106 (27.2)	.275	0.059
COPD	31 (2.9)	25 (2.5)	6 (1.5)	.357	0.060
Asthma	38 (3.5)	52 (5.1)	22 (5.6)	.098	0.068
Creatinine	98.00 (21.85)	96.74 (20.95)	95.07 (20.31)	.056	0.093
LVEF <50%	273 (25.2)	221 (21.9)	109 (27.9)	.039	0.094
PVD	73 (6.7)	72 (7.1)	21 (5.4)	.501	0.048
AF	18 (1.7)	13 (1.3)	4 (1.0)	.602	0.037
MI	481 (44.4)	398 (39.4)	161 (41.3)	.068	0.067
Cerebrovascular disease	31 (2.9)	35 (3.5)	5 (1.3)	.089	0.096
Hypertension	852 (78.6)	758 (75.0)	303 (77.7)	.147	0.056
Hyperlipidemia	1016 (93.7)	949 (94.0)	364 (93.3)	.908	0.017
RCA	876 (80.8)	871 (86.2)	264 (67.7)	<.001	0.301
Off-pump	413 (38.1)	403 (39.9)	175 (44.9)	.064	0.092

Values are presented as mean (± standard deviation) or n (%). *SAG*, Single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft; *SMD*, standardized mean difference; *NYHA*, New York Heart Association; *COPD*, chronic obstructive pulmonary disease; *LVEF*, left ventricle ejection fraction; *PVD*, peripheral vascular disease; *AF*, atrial fibrillation; *MI*, myocardial infarction; *RCA*, right coronary artery.

TABLE 2. Patients characteristics in the PS-weighted sample

	SAG	MAG	TAG	*P* value	SMD
n	1084.00	941	843		
Age	64 (9)	64 (9)	64 (9)	.953	0.011
Nonwhite	93 (8.6)	74 (7.9)	42 (4.9)	.054	0.098
Female sex	145 (13.4)	110 (11.7)	121 (14.4)	.407	0.054
NYHA functional class 3-4	224 (20.7)	195 (20.8)	142 (16.9)	.200	0.067
Diabetes	253 (23.3)	215 (22.8)	201 (23.8)	.916	0.015
COPD	31 (2.9)	25 (2.7)	11 (1.3)	.193	0.072
Asthma	38 (3.5)	32 (3.4)	25 (3.0)	.799	0.020
Creatinine	98 (22)	98 (20)	97 (20)	.835	0.022
LVEF <50%	273 (25.2)	225 (23.9)	226 (26.8)	.523	0.045
PVD	73 (6.7)	66 (7.0)	56 (6.7)	.965	0.008
AF	18 (1.7)	12 (1.3)	6 (0.8)	.311	0.055
MI	481 (44.4)	403 (42.9)	366 (43.4)	.840	0.020
Cerebrovascular disease	31 (2.9)	30 (3.2)	13 (1.5)	.230	0.074
Hypertension	852 (78.6)	729 (77.5)	662 (78.5)	.857	0.018
Hyperlipidemia	1016 (93.7)	889 (94.4)	785 (93.2)	.652	0.035
RCA	876 (80.8)	776 (82.5)	665 (78.8)	.299	0.062
Off-pump	413 (38.1)	349 (37.1)	330 (39.1)	.757	0.028

Values are presented as mean (± standard deviation) or n (%). *SAG*, Single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft; *SMD*, standardized mean difference; *NYHA*, New York Heart Association; *COPD*, chronic obstructive pulmonary disease; *LVEF*, left ventricle ejection fraction; *PVD*, peripheral vascular disease; *AF*, atrial fibrillation; *MI*, myocardial infarction; *RCA*, right coronary artery.

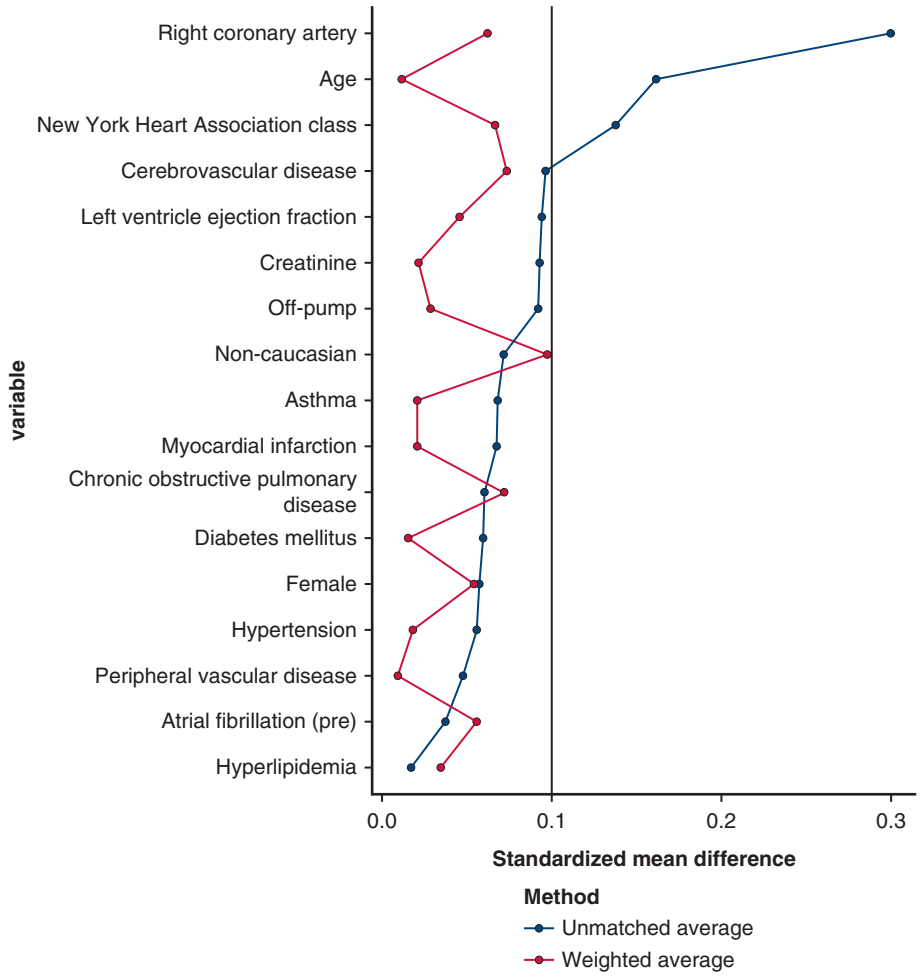

FIGURE 1. The Love plot shows the changes in standardized mean difference before and after matching. It demonstrates that the balance of covariates was improved on all variables, which are below the threshold of 0.1 of absolute mean difference.

mortality and the composite of death, MI, stroke, and revascularization. In the TAG group, this difference became statistically significant.

For each patient, we calculated the TAG index, which is an intuitive index of the proportion of revascularization achieved with arterial grafts. We found that there was a liner relationship between the TAG index and the risk reduction in 10-year mortality and composite endpoint.

Despite recent advances in secondary prevention following CABG, including statin therapy and dual antiplatelet therapy,[12] long-term SVG patency rates still remain inferior to those of arterial grafts.[2,3] SVG failure can occur in up to 40% of patients and it is associated with a significantly increased risk of the composite of adverse events.[13] However, SVG is still widely used during CABG not only to supplement the SITA graft but also when additional arterial grafts are used.[14] The exclusive use of arterial grafts is perceived as technically more demanding[15] and remains largely underused.[14] This is partially due to the limited evidence supporting the superiority of TAG over other revascularization strategies using SVG. A recent meta-analysis of 4 small randomized controlled trials[16] with short-term follow-up, plus 21 observational studies found that when compared with no-TAG, TAG was associated with reduced long-term all-cause mortality in observational studies matched/adjusted for confounders (incident rate ratio 0.85; 95% CI, 0.81-0.89, $P = .0001$; $I^2 = 0\%$) and unmatched/unadjusted (incident rate ratio 0.67; 95% CI, 0.59-0.76, $P = .0001$; $I^2 = 67\%$). Decreases in major cardiovascular outcomes and revascularization did not achieve statistical significance. Moreover, when compared with patients with 2 arterial grafts, TAG was still associated with reduced long-term all-cause mortality (incident rate ratio, 0.85; 95% CI, 0.73-0.99, $P = .04$) with minimal heterogeneity ($I^2 = 5\%$).

The ART trial was designed to compare 10-year survival after BITA versus SITA grafts. No significant differences were found at 10 years between the 2 groups according to the intention-to-treat analysis.[10] However, the relatively

TABLE 3. Treatment effect estimation

	10-y cumulative incidence, %	Hazard ratio (95% CI)	*P* value
All-cause death (*P* trend = .02)			
SAG	24.6	Ref	
MAG	21.1	0.84 (0.69-1.03)	.09
TAG	18.4	0.68 (0.48-0.96)	.03
MI (*P* trend = .43)			
SAG	5.5	Ref	
MAG	4.8	0.85 (0.55-1.32)	.47
TAG	5.2	0.82 (0.45-1.47)	.50
Revascularization (*P* = .04)			
SAG	11.3	Ref	
MAG	11.3	0.82 (0.61-1.12)	.22
TAG	10.1	0.64 (0.41-1.00)	.05
Stroke (*P* trend = .65)			
SAG	5.6	Ref	
MAG	4.4	0.83 (0.53-1.30)	.42
TAG	5.7	1.29 (0.57-2.92)	.53
Death/MI/stroke/revascularization (*P* trend = .01)			
SAG	37.0	Ref	
MAG	32.1	0.82 (0.69-0.96)	.02
TAG	31.4	0.71 (0.53-0.94)	.02

CI, Confidence interval; *SAG*, single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft; *MI*, myocardial infarction.

high rate of crossover (14%) may have influenced these results, and an exploratory analysis supported the hypothesis that patients receiving 2 or more arterial grafts was associated with a lower risk of mortality. However, a large proportion of patients receiving additional arterial grafts were also treated with SVG to complete surgical revascularization, and what remains unclear is whether the exclusive use of arterial grafts was associated with a further benefit.

The present post-hoc analysis of the ART trial showed that both MAG with additional SVG and TAG were associated with a numerically lower incidence of adverse events (mortality and composite of mortality, MI, stroke, and/or revascularization) but TAG was associated with a larger and statistically significant advantage. In particular, TAG was associated with a significant reduction of 10-year mortality and rate of repeat revascularization. When analysis was restricted to high-risk subgroups, TAG and MAG strategies were beneficial in patients with insulin-dependent diabetes but not in patients older than 70 years. These results are supported by a recent study from New York State,[17] which reported that MAG was beneficial only in patients younger than 70 years old but not in patients with diabetes. However this analysis did not discriminate between insulin-dependent and orally treated subjects.

We also found an inverse association between the risk of 10-year adverse events and the proportion of revascularization achieved with arterial grafts (TAG index).

Although the present comparison is observational in nature, PS-weighed groups were comparable for all relevant characteristics. Moreover, it should be noted that patients enrolled in a trial are more homogeneous than those from observational cohorts.

Despite this, however, the main limitation of the present analyses is that it remains a nonrandomized comparison. While PS modeling included all baseline variables, we cannot exclude a residual selection bias based on unmeasured or unmeasurable characteristics. Moreover, assessment of extension and severity of native coronary disease

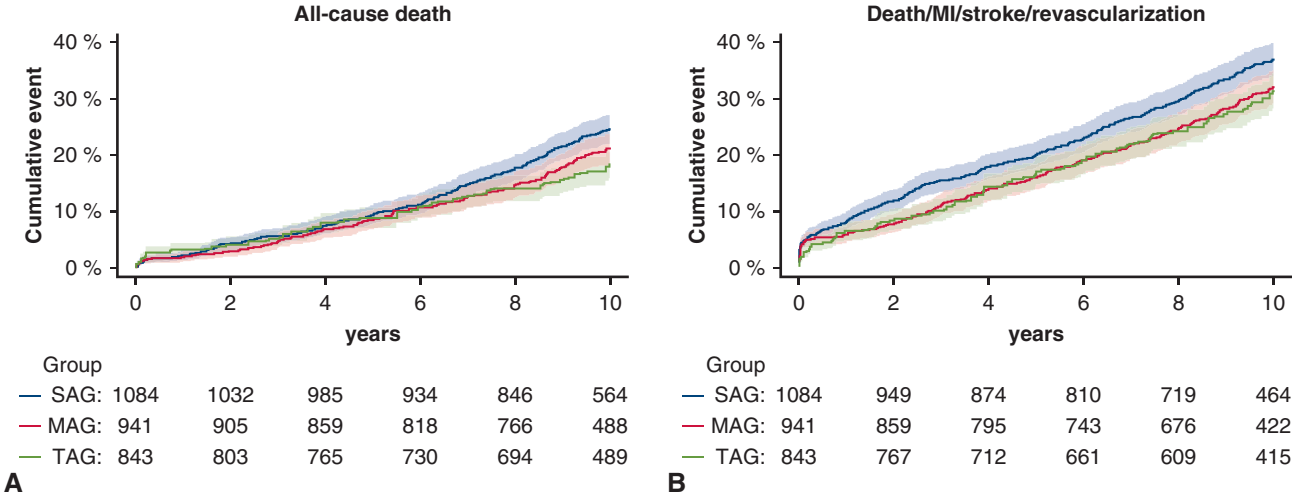

FIGURE 2. A, Kaplan–Meier curves showing cumulative 10-year mortality in the 3 groups after IPTW. The confidence limit of each curve is shown as a *shaded area*. B, Kaplan–Meier curves show cumulative 10-year incidence of composite of death, MI, stroke, and repeat revascularization in the 3 groups after IPTW. The confidence limit of each curve is shown as a *shaded area*. *SAG*, Single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft.

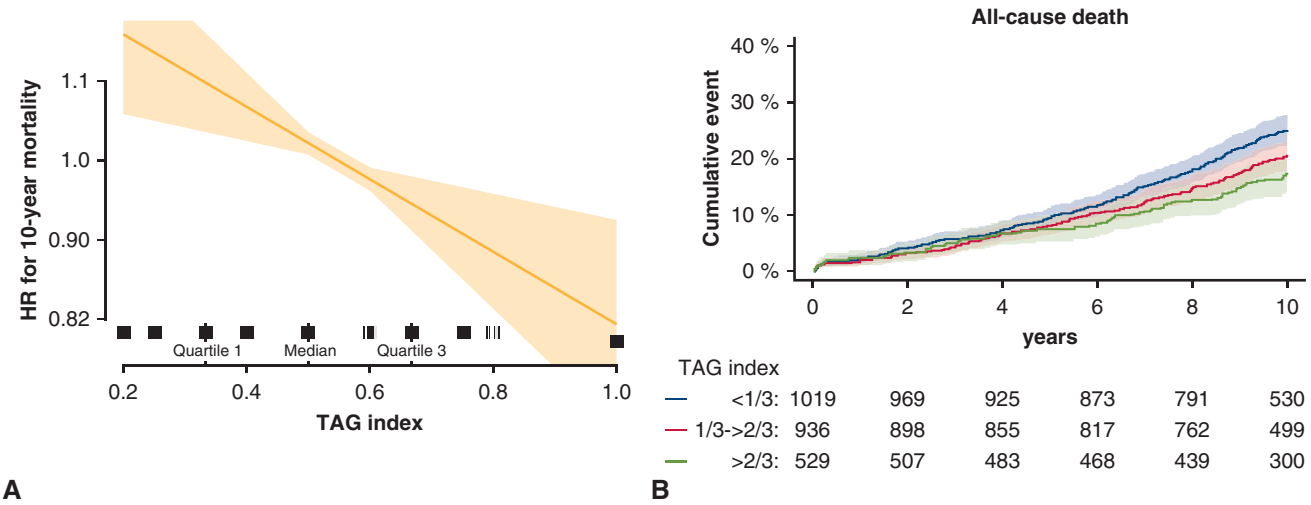

FIGURE 3. A, Linear relationship between the TAG index and the risk of 10-year mortality. TAG index median (0.5) as reference. B, Kaplan–Meier curve show cumulative 10-year mortality according to the TAG index. The confidence limit of each curve is shown as a *shaded area*. *HR*, Hazard ratio; *TAG*, total arterial graft.

TABLE 4. Multivariable Cox regression to test the association between the TAG index and outcomes of interest

Variable	10-y mortality HR (95% CI)	*P* value	10-y MACE HR (95% CI)	*P* value
TAG index				
≤1/3	Ref		Ref	
1/3-2/3	0.85 (0.70-1.04)	.11	0.84 (0.72-0.99)	.03
>2/3	0.73 (0.57-0.93)	.01	0.75 (0.62-0.92)	.004
Continuous	0.68 (0.47-0.97)	.03	0.68 (0.51-0.90)	.007
Age	1.07 (1.06-1.08)	<.001	1.03 (1.02-1.04)	<.001
Nonwhite	0.72 (0.46-1.11)	.13	0.76 (0.56-1.04)	.08266
Female	0.96 (0.74-1.24)	.73	1.17 (0.96-1.44)	.11558
NYHA functional class	1.11 (0.90-1.38)	.33	1.15 (0.97-1.37)	.10295
DM	1.33 (1.10-1.61)	.004	1.15 (0.98-1.35)	.07996
COPD	1.14 (0.72-1.80)	.57	1.09 (0.73-1.62)	.67814
Asthma	1.32 (0.90-1.92)	.15	1.64 (1.23-2.19)	<.001
Creatinine	1.01 (1.00-1.01)	<.001	1.00 (1.00-1.01)	.03723
LVEF	1.76 (1.46-2.12)	<.001	1.28 (1.09-1.50)	.00232
PVD	1.35 (1.02-1.80)	.04	1.39 (1.09-1.77)	.00715
AF	2.14 (1.35-3.39)	.001	1.71 (1.10-2.66)	.01710
MI	1.09 (0.91-1.30)	.35	1.08 (0.93-1.24)	.31520
CVD	1.49 (1.01-2.19)	.04	1.35 (0.96-1.90)	.08392
Hypertension	1.22 (0.96-1.54)	.10	1.16 (0.97-1.39)	.11294
Hyperlipidemia	0.94 (0.66-1.34)	.73	0.86 (0.65-1.13)	.27583
RCA	1.08 (0.85-1.35)	.54	1.04 (0.87-1.25)	.66037
Off-pump	1.08 (0.90-1.30)	.41	1.00 (0.86-1.17)	.96181

MACE, Major adverse cardiac events; *HR*, hazard ratio; *CI*, confidence interval; *TAG*, total arterial graft; *NYHA*, New York Heart Association; *DM*, diabetes mellitus; *COPD*, chronic obstructive pulmonary disease; *LVEF*, left ventricle ejection fraction; *PVD*, peripheral vascular disease; *AF*, atrial fibrillation; *MI*, myocardial infarction; *CVD*, cerebrovascular disease; *RCA*, right coronary artery.

was based on qualitative surgeon assessment and not on the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score.

In the ART when patients were randomized between 2004 and 2007, the only formal exclusion criteria were patients requiring a single graft, redo patients, or those with evidence of an evolving MI. However, the ART population may now, by current standards, be considered low risk for CABG and their generalizability to a contemporary cohort of patients, who are more likely to be older and sicker, remains to be determined.

In addition, the impact of surgeon expertise in ART has been addressed in a previous paper using the BITA conversion of BITA to SITA rate as a proxy of surgical expertise.[18] This approach could not be replicated in the present study due to the lack of information regarding the use of radial artery. However, to account for the potential influence of individual surgeon experience, our modeling of outcomes was stratified according to the surgeon performing the operation and results showed a favorable effect of TAG on 10-year incidence of death and of both MAG and TAG on the composite of death, stroke, MI, and revascularization.

In conclusion, the present post-hoc ART analysis showed that in ART there was an increasing benefit on 10-year outcomes by increasing the extension of arterial revascularization. As a consequence, MAG and TAG were associated with lower incidence of adverse events but TAG was associated with the greatest benefit. These findings support the hypothesis that both MAG and TAG represent valuable strategies to improve clinical outcomes following CABG but TAG can potentially provide further benefit in an appropriately selected population. Further studies, including

the ongoing ROMA trial,[19] are necessary to provide final evidence into the potential benefit of total arterial revascularization.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: coronary artery bypass, CABG, single arterial graft, multiple arterial grafts, total arterial grafts

TABLE E1. Graft configuration

Group	SAG	MAG			TAG	
Total, n	1084	1010			390	
Graft configuration	SITA+SVG	BITA+SVG	SITA+RA+SVG	BITA+RA+SVG	BITA only	SITA+RA	BITA+RA
n (%)	1084 (100.0)	775 (100.0)	189 (100.0)	46 (100.0)	62 (100.0)	101 (100.0)	227 (100.0)
Sequential, n (%)	195 (18.0)	134 (17.3)	44 (23.3)	6 (13.0)	62 (96.8)	77 (76.2)	69 (30.4)

SAG, Single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft; *SITA*, single internal thoracic artery; *SVG*, saphenous vein graft; *BITA*, bilateral internal thoracic artery; *RA*, radial artery.

TABLE E2. Compliance with goal-directed medical therapy in the 3 groups

	SAG, %	MAG,%	TAG, %
n	593 (54.7)	625 (61.9)	240 (61.5)
Aspirin	80.6	81.3	83.3
Statins	91.3	91.0	88.0
Angiotensin-converting enzyme inhibitors	54.3	56.7	59.0
Beta-blockers	77.3	72.5	68.3

SAG, Single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft.

TABLE E3. Standardized mean difference between individual group comparison before and after IPTW

	Unmatched average	Unmatched SAG vs MAG	Unmatched SAG vs MAG	Unmatched MAG vs TAG	Weighted average	Weighted SAG vs MAG	Weighted SAG vs TAG	Weighted MAG vs TAG
Age	0.16	0.09	0.24	0.16	0.01	0.01	0.005	0.02
Female	0.06	0.05	0.04	0.09	0.05	0.05	0.03	0.08
DM	0.06	0.003	0.09	0.09	0.01	0.01	0.01	0.02
COPD	0.06	0.02	0.09	0.07	0.07	0.01	0.11	0.10
Asthma	0.07	0.08	0.10	0.02	0.02	0.004	0.03	0.03
Creatinine	0.09	0.06	0.14	0.08	0.02	0.02	0.03	0.01
LVEF	0.09	0.08	0.06	0.14	0.05	0.03	0.04	0.07
PVD	0.05	0.02	0.06	0.07	0.008	0.009	0.003	0.01
AF	0.04	0.03	0.06	0.02	0.06	0.03	0.08	0.05
MI	0.07	0.10	0.06	0.04	0.02	0.03	0.02	0.01
RCA	0.30	0.15	0.30	0.45	0.06	0.04	0.05	0.09
Off-pump	0.09	0.04	0.14	0.10	0.03	0.02	0.02	0.04
Nonwhite	0.07	0.01	0.09	0.10	0.10	0.03	0.15	0.12
NYHA functional class	0.14	0.07	0.14	0.21	0.07	0.0027	0.10	0.10
Hypertension	0.06	0.	0.02	0.06	0.02	0.03	0.003	0.02
Hyperlipidemia	0.02	0.01	0.02	0.03	0.03	0.03	0.02	0.05
CVD	0.10	0.03	0.11	0.14	0.07	0.02	0.09	0.11

SAG, Single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft; *DM*, diabetes mellitus; *COPD*, chronic obstructive pulmonary disease; *LVEF*, left ventricle ejection fraction; *PVD*, peripheral vascular disease; *AF*, atrial fibrillation; *MI*, myocardial infarction; *RCA*, right coronary artery; *NYHA*, New York Heart Association; *CVD*, cerebrovascular disease.

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TABLE E4. Comparison of cardiac versus noncardiac cause of death in the 3 groups

	SAG	MAG	TAG	*P* value
n (%)	1084	941	843	
Cardiovascular death	91 (8.4)	74 (7.8)	55 (6.5)	.220
Noncardiovascular death	165 (15.2)	118 (12.5)	95 (11.3)	

SAG, Single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft.

TABLE E5. Incidence of sternal wound infection requiring reconstruction in the groups

	SAG	MAG	TAG	*P* value
n (%)	1084	941	843	
Sternal wound infection	4 (15.4)	8 (20.7)	6 (11.0)	.60

SAG, Single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft.

TABLE E6. Treatment effect estimation in patients older than 70 years old

	10-y cumulative incidence, %	Hazard ratio (95% CI)	*P* value
All-cause death (*P* trend = .15)			
SAG	41.7	Ref	
MAG	37.8	0.91 (0.66-1.25)	.55
TAG	29.3	0.67 (0.39-1.17)	.16
Death/MI/stroke/ revascularization (*P* trend = .09)			
SAG	51.3	Ref	
MAG	47	0.95 (0.72-1.25)	.70
TAG	42.3	0.65 (0.40; 1.07)	.09

CI, Confidence interval; *SAG*, single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft; *MI*, myocardial infarction.

TABLE E7. Treatment effect estimation in insulin-dependent patients with diabetes

	10-y cumulative incidence, %	Hazard ratio (95% CI)	*P* value
All-cause death (*P*-trend = .02)			
SAG	24.6	Ref	
MAG	21.1	0.84 (0.69-1.03)	.10
TAG	18.4	0.68 (0.48-0.96)	.03
Death/MI/stroke/ revascularization (*P*-trend = .007)			
SAG	37.0	Ref	
MAG	32.1	0.82 (0.69-0.96)	.02
TAG	31.4	0.71 (0.53-0.94)	.02

CI, Confidence interval; *SAG*, single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft; *MI*, myocardial infarction.

TABLE E8. Multivariable Cox model stratified by number of grafts

Variable	10-y mortality		10-y MACE	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Group*,†				
SAG	Ref		Ref	
MAG	0.86 (0.71-1.04)	.12	0.83 (0.71-0.97)	.01
TAG	0.77 (0.58-0.97)	.04	0.78 (0.63-0.97)	.02
Age	1.07 (1.06-1.08)	<.001	1.03 (1.02-1.04)	<.001
Nonwhite	0.73 (0.47-1.13)	.16	0.77 (0.57-1.05)	.10
Female	0.93 (0.72-1.20)	.57	1.15 (0.94-1.41)	.17
NYHA functional class	1.10 (0.89-1.36)	.40	1.15 (0.97-1.36)	.11
DM	1.33 (1.10-1.62)	.003	1.15 (0.98-1.35)	.08
COPD	1.16 (0.74-1.84)	.51	1.08 (0.73-1.61)	.69
Asthma	1.31 (0.90-1.92)	.16	1.66 (1.25-2.22)	<.001
Creatinine	1.01 (1.00-1.01)	<.001	1.00 (1.00-1.01)	.034
LVEF	1.76 (1.46-2.12)	<.001	1.28 (1.09-1.50)	.002
PVD	1.38 (1.03-1.83)	.03	1.40 (1.10-1.78)	.006
AF, pre	2.20 (1.39-3.48)	<.001	1.74 (1.12-2.71)	.01
MI	1.09 (0.91-1.31)	.33	1.08 (0.93-1.25)	.30
CVD	1.52 (1.03-2.24)	.03	1.37 (0.98-1.93)	.07
Hypertension	1.21 (0.96-1.53)	.10	1.16 (0.96-1.38)	.12
Hyperlipidemia	0.96 (0.67-1.37)	.80	0.87 (0.66-1.15)	.32
RCA	1.13 (0.90-1.43)	.30	1.08 (0.89-1.30)	.44
Off-pump	1.09 (0.91-1.32)	.35	1.01 (0.87-1.17)	.90

MACE, Major adverse cardiac events; *HR*, hazard ratio; *CI*, confidence interval; *SAG*, single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft; *NYHA*, New York Heart Association; *DM*, diabetes mellitus; *COPD*, chronic obstructive pulmonary disease; *LVEF*, left ventricle ejection fraction; *PVD*, peripheral vascular disease; *AF*, atrial fibrillation; *MI*, myocardial infarction; *CVD*, cerebrovascular disease; *RCA*, right coronary artery. **P* value for test for trend = .03 for mortality. †*P* value for test for trend = .006 for MACE.

TABLE E9. Treatment effect estimation of MAG/TAG group versus SAG according to multivariable model and without propensity score

	10-y cumulative incidence, %	Hazard ratio (95% CI)	*P* value
All-cause death			
SAG	24.6	Ref	
MAG/TAG	19.5	0.78 (0.65-0.92)	.004
MI			
SAG	5.5	Ref	
MAG/TAG	4.9	0.85 (0.59-1.22)	.38
Revascularization			
SAG	11.3	Ref	
MAG/TAG	10.8	0.91 (0.71-1.18)	.49
Stroke			
SAG	5.6	Ref	
MAG/TAG	4.2	0.73 (0.50-1.07)	.10
Death/MI/stroke/ revascularization			
SAG	37.0	Ref	
MAG/TAG	30.8	0.79 (0.68-0.90)	<.001

CI, Confidence interval; *SAG*, single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft; *MI*, myocardial infarction.

TABLE E10. Treatment effect estimation in the overall population without adjustment

	10-y cumulative incidence, %	Hazard ratio (95% CI)	*P* value
All-cause death (P trend = .003)			
SAG	24.6	Ref	
MAG	20.2	0.80 (0.67-0.97)	.02
TAG	17.9	0.71 (0.54-0.93)	.01
MI (P trend = .33)			
SAG	5.5	Ref	
MAG	5.0	0.88 (0.60-1.30)	.53
TAG	4.6	0.77 (0.44-1.35)	.37
Revascularization (P = .35)			
SAG	11.3	Ref	
MAG	11.1	0.95 (0.72-1.24)	.70
TAG	9.9	0.83 (0.56-1.21)	.33
Stroke (P trend = .09)			
SAG	5.6	Ref	
MAG	4.3	0.76 (0.51-1.15)	.20
TAG	3.7	0.64 (0.35-1.18)	.15
Death/MI/stroke/ revascularization (P trend = .001)			
SAG	37.0	Ref	
MAG	31.1	0.80 (0.68-0.92)	.003
TAG	30.2	0.76 (0.62-0.94)	.01

CI, Confidence interval; *SAG*, single arterial graft; *MAG*, multiple arterial graft; *TAG*, total arterial graft; *MI*, myocardial infarction.

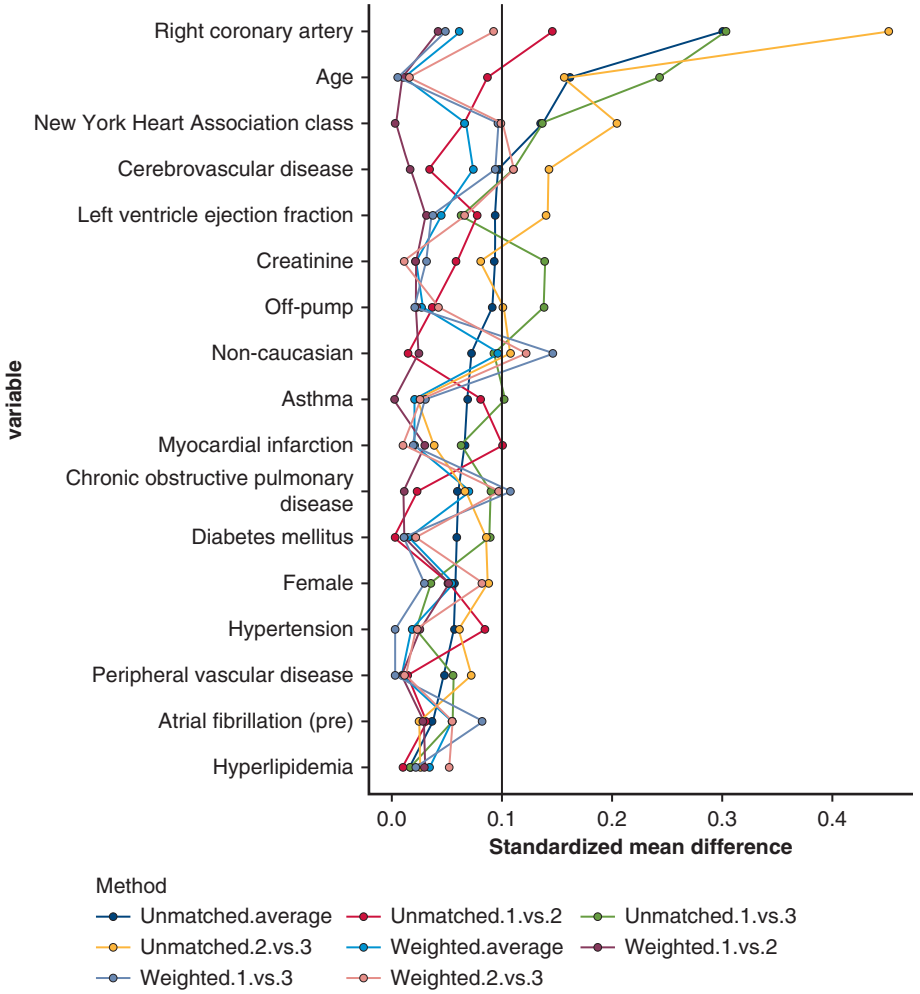

FIGURE E1. Standardized mean difference before and after inverse probability of treatment weighting for each comparison (1: SAG; 2: MAG; 3: TAG).

ADULT

000 Effect of total arterial grafting in the Arterial Revascularization Trial

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When compared with single arterial grafting, both multiple and total arterial grafting represent valuable strategies to improve clinical outcomes following coronary artery bypass but total arterial grafting can potentially provide further benefit.