Effect of Total Arterial Grafting in the Arterial Revascularization Trial

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Abbreviations

ART: Arterial revascularization trial

ATT: average treatment effect on the treated

BITA: Bilateral internal thoracic arteries

CABG: coronary artery bypass grafting

COPD: chronic obstructive pulmonary disease

IPTW: inverse probability of treatment weighting

LVEF: left ventricular ejection fraction

MAG: multiple arterial graft

MI: myocardial infarction

PCI: percutaneous coronary intervention

PVD: peripheral vascular disease

PS: propensity score

RA: radial artery

RCA: right coronary artery

SAG: single arterial graft

SITA: Single internal thoracic artery

SVG: saphenous vein graft

SMD: standardized mean difference

TAG: total arterial graft

Abstract

Background: The Arterial Revascularization Trial (ART) was designed to compare 10 years survival in bilateral (BITA) vs. single internal thoracic artery (SITA) grafts. The intention to treat analysis has showed comparable outcomes between the two 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). Among 3102 patients enrolled in ART, only those receiving at least 3 grafts were included. Patients receiving single arterial graft (SAG) plus saphenous vein graft (SVG) were included in the SAG group; patients receiving 2 or more arterial grafts with additional SVG were included in the multiple arterial graft (MAG) group; patients receiving arterial grafts only were included in the total arterial graft (TAG) group. Inverse probability of treatment weighting (IPTW) was used for comparison.

Results: The final population consisted of 1084, 1010 and 390 patients in the SAG, MAG and TAG group respectively. IPTW analysis showed that when compared to 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=0.02) and TAG group was associated with the lowest risk of late mortality (HR 0.68; 95% CI 0.48-0.96;P=0.03). TAG was also associated with a significant risk reduction of the composite of death/MI/stroke and repeat revascularization (HR 0.71; 95%CI 0.53-0.94; P=0.02).

Conclusions: When compared to SAG, both MAG and TAG represent valuable strategies to improve clinical outcomes following CABG but TAG can potentially provide further benefit.

Introduction

Graft failure after coronary artery bypass grafting (CABG) causes recurrent angina, need for repeat intervention and poorer survival [1]. Arterial grafts (AG) including bilateral internal thoracic artery (BITA) grafts and/or the radial artery (RA) have been consistently shown to provide superior angiographic patency rates when compared to saphenous vein grafts (SVG) [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 underutilised to supplement a single arterial graft (SAG) and multiple arterial graft (MAG) strategies.

The Arterial Revascularization Trial (ART) was designed to compare 10 years survival in bilateral (BITA) vs. single internal thoracic artery (SITA) grafts. The intention to treat analysis has shown comparable outcomes between the two 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)

Material and 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 a single arterial graft (SAG) plus saphenous vein graft (SVG) were included in the SAG group; patients receiving 2 or more arterial grafts with additional SVG were included in the multiple arterial graft (MAG) group; patients receiving arterial grafts only included in the total arterial graft (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 single internal thoracic artery 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]. Briefly, 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/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 post-operative 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, myocardial infarction, 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 four characteristics for each graft performed: quality of the target (1 to 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 non-cardiovascular causes, where possible, using autopsy reports and death certificates. Congestive heart failure, arrhythmia or myocardial infarction, 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 two of the following three criteria were present: 1. Unequivocal ECG 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 which lasted more than 20 minutes. Stroke was defined as new neurological 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 CT or MRI scan of recent brain infarct (less than 6 months). Repeat revascularization was defined as coronary bypass surgery or percutaneous coronary intervention (PCI) 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 model. The mean and the most frequent value were used to impute continuous and categorical variables, respectively. To compare the three groups, inverse probability of treatment weighting (IPTW) was used and the treatment effect on the treated (ATT) was estimated to draw inferences about the relative effectiveness of the three treatment groups. For this purpose, a generalized boosted model was implemented to estimate propensity scores (PS) adjusting for pre-treatment covariates, age, female sex, diabetes, chronic obstructive pulmonary disease (COPD), asthma, creatinine, left ventricular ejection fraction (LVEF), peripheral vascular disease (PVD), pre-operative atrial fibrillation (AF), myocardial infarction (MI), right coronary artery (RCA) disease, off-pump status, race, NYHA functional class, hypertension, hyperlipaemia, cerebrovascular disease. The propensity score was assumed as the probability that an individual with pre-treatment characteristics X receives SAG (twang R package). We gave each treatment case a weight of 1 and each comparison case a weight $w_i = p(x_i)/(1 - p(x_i))$. The absolute standardised mean difference (SMD) was used as a balance metric to summarize the difference between two univariate distributions of a single pre-treatment 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 (i.e., 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 utilize an outcomes regression model and propensity scores are "doubly robust" in the sense that if either the propensity score 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). Sub-distribution HR were calculated for non-fatal 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) while TAG index =0 corresponds to revascularization with SVG only. By forcing the TAG index (as a continuous and categorial variable as $< \frac{1}{3}; \frac{1}{3}\ to \frac{2}{3}; > \frac{2}{3}$) 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 hazard ratio (HR) and 95% confidence interval (95%CI) using the median value of TAG index as reference.

All p-values <0.05 were considered as indicating statistical significance. 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 summarised in Supplementary Table 1. The three groups presented some differences in baseline characteristics (Table 1, average SMD>0.10). In particular, patients in the TAG group were 2 years younger on average and were less likely to have a concomitant RCA disease, a worse NYHA functional class but more likely to have an LVEF <50%. Guideline directed medical therapy at 10 years is shown in Supplementary Table 4. PS weighting created 3 groups comparable for all baseline characteristics (Table 2, Figure 1, Supplementary Table 2 and Supplementary Figure 2). The distinction between cardiovascular and non-cardiovascular cause of death is presented in Supplementary Table 5, and supplementary Table 6 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 three groups (test for trend =0.02; Figure 2A) and TAG was associated with a significant risk reduction of all-cause death when compared to SAG (HR 0.68; 95% CI 0.48-0.96;P=0.03). The same trend was observed for the revascularization (P=0.04) and the composite of death/MI/stroke and repeat revascularization (P=0.01) 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=0.02; Figure 2B) when compared to SAG.

The results of analysis in patients older than 70 years old and insulin-dependent diabetic patients are depicted in supplementary Tables 7, 8. 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 insulin-dependent diabetic patients. Multivariable Cox models (Supplementary Table 3) confirmed that when compared to 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 (Supplementary Table 9). Supplementary Table 10 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=0.03) and composite outcome (HR 0.68; 95%CI 0.51-0.90;P=0.007, Figure 3A and Figure 3B; Table 4). When the TAG index was used as categorial variable, when compared to cases with TAG index $<\frac{1}{3}$, a larger proportion of arterial revascularization (TAG index between $\frac{1}{3}$ and $\frac{2}{3}$ or TAG index $> \frac{2}{3}$) 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 to SAG, MAG group showed a numerically lower rate of 10-year 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 underutilized [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 four small randomized controlled trials [16] with short term follow-up, plus 21 observational studies found that when compared to 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 = 0.0001; I2 =0%) and unmatched/unadjusted (incident rate ratio 0.67, 95% CI: 0.59–0.76, p = 0.0001; I2 = 67%). Decreases in major cardiovascular outcomes and revascularization did not achieve statistical significance. Moreover, when compared to patients with two 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=0.04) with minimal heterogeneity (I2=5%).

The ART trial was designed to compare 10-year survival after BITA vs 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 high rate of cross-over (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 it 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 reporting that MAG was beneficial only in patients younger than 70 years old but not in diabetic patients. 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, propensity score 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 non randomized comparison. While propensity score modelling 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 was based on qualitative surgeon assessment and not on the SYNTAX score.

In the ART when patients were randomized between 2004-2007 the only formal exclusion criteria were patients requiring a single graft, redo patients or those with evidence of an evolving myocardial infarction. 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.

Additionally, 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 modelling of outcomes was stratified according to the surgeon performing the operation and results showed a favourable effect of TAG on 10-year incidence of death and of both MAG and TAG on the composite of death, stroke, myocardial infarction 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 in order 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.

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Figure legends

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.

Figure 2A. Kaplan-Meier curves showing cumulative 10-year mortality in the three groups after inverse probability of treatment weighting (IPTW). The confidence limit of each curve is shown as shaded area. SAG single arterial graft, MAG multiple arterial graft, TAG total arterial graft.

Figure 2B. Kaplan-Meier curves show cumulative 10-year incidence of composite of death, MI, stroke and repeat revascularization in the three groups after inverse probability of treatment weighting (IPTW). The confidence limit of each curve is shown as shaded area. SAG single arterial graft, MAG multiple arterial graft, TAG total arterial graft.

Figure 3A. Linear relationship between the TAG index and the risk of 10-year mortality. TAG index median (0.5) as reference.

Figure 3B. Kaplan-Meier curve show cumulative 10-year mortality according to the TAG index. The confidence limit of each curve is shown as shaded area.

Supplementary Figure 1. Standardized mean difference before and after inverse probability of treatment weighting for each comparison (1: single arterial graft (SAG), 2: multiple arterial graft (MAG); 3: total arterial graft (TAG)).

Table 1. Patients characteristics in the original sample

	SAG	MAG	TAG	P-value	SMD
n	1084	1010	390		
Age	64.20 (8.92)	63.42 (8.86)	62.03 (8.95)	<0.001	0.162
Non-Caucasian	93 (8.6)	91 (9.0)	24 (6.2)	0.213	0.072
Female gender	145 (13.4)	118 (11.7)	57 (14.6)	0.276	0.058
NYHA functional class 3-4	224 (20.7)	237 (23.5)	60 (15.4)	0.004	0.137
Diabetes	253 (23.3)	237 (23.5)	106 (27.2)	0.275	0.059
COPD	31 (2.9)	25 (2.5)	6 (1.5)	0.357	0.060
Asthma	38 (3.5)	52 (5.1)	22 (5.6)	0.098	0.068
Creatinine	98.00 (21.85)	96.74 (20.95)	95.07 (20.31)	0.056	0.093
LVEF<50%	273 (25.2)	221 (21.9)	109 (27.9)	0.039	0.094
PVD	73 (6.7)	72 (7.1)	21 (5.4)	0.501	0.048
AF	18 (1.7)	13 (1.3)	4 (1.0)	0.602	0.037
MI	481 (44.4)	398 (39.4)	161 (41.3)	0.068	0.067
Cerebrovascular disease	31 (2.9)	35 (3.5)	5 (1.3)	0.089	0.096
Hypertension	852 (78.6)	758 (75.0)	303 (77.7)	0.147	0.056
Hyperlipidemia	1016 (93.7)	949 (94.0)	364 (93.3)	0.908	0.017
RCA	876 (80.8)	871 (86.2)	264 (67.7)	<0.001	0.301
Off-pump	413 (38.1)	403 (39.9)	175 (44.9)	0.064	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)	0.953	0.011
Non-Caucasian	93 (8.6)	74 (7.9)	42 (4.9)	0.054	0.098
Female gender	145 (13.4)	110 (11.7)	121 (14.4)	0.407	0.054
NYHA functional class 3-4	224 (20.7)	195 (20.8)	142 (16.9)	0.200	0.067
Diabetes	253 (23.3)	215 (22.8)	201 (23.8)	0.916	0.015
COPD	31 (2.9)	25 (2.7)	11 (1.3)	0.193	0.072
Asthma	38 (3.5)	32 (3.4)	25 (3.0)	0.799	0.020
Creatinine	98 (22)	98 (20)	97 (20)	0.835	0.022
LVEF<50%	273 (25.2)	225 (23.9)	226 (26.8)	0.523	0.045
PVD	73 (6.7)	66 (7.0)	56 (6.7)	0.965	0.008
AF	18 (1.7)	12 (1.3)	6 (0.8)	0.311	0.055
MI	481 (44.4)	403 (42.9)	366 (43.4)	0.840	0.020
Cerebrovascular disease	31 (2.9)	30 (3.2)	13 (1.5)	0.230	0.074
Hypertension	852 (78.6)	729 (77.5)	662 (78.5)	0.857	0.018
Hyperlipidemia	1016 (93.7)	889 (94.4)	785 (93.2)	0.652	0.035
RCA	876 (80.8)	776 (82.5)	665 (78.8)	0.299	0.062
Off-pump	413 (38.1)	349 (37.1)	330 (39.1)	0.757	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.

Table 3. Treatment effect estimation

		10-y cumulative incidence	HazardRatio	CI.95	p-value
All-cause death (P-trend=0.02)					
	SAG	24.6%	Ref		
	MAG	21.1%	0.84	[0.69;1.03]	0.09
	TAG	18.4%	0.68	[0.48;0.96]	0.03
MI (P-trend=0.43)					
	SAG	5.5%	Ref		
	MAG	4.8%	0.85	[0.55;1.32]	0.47
	TAG	5.2%	0.82	[0.45;1.47]	0.50
Revascularization (P=0.04)					
	SAG	11.3%	Ref		
	MAG	11.3%	0.82	[0.61;1.12]	0.22
	TAG	10.1%	0.64	[0.41;1.00]	0.05
STROKE (P-trend=0.65)					
	SAG	5.6%	Ref		
	MAG	4.4%	0.83	[0.53;1.30]	0.42
	TAG	5.7%	1.29	[0.57;2.92]	0.53
Death/MI/STROKE/revascularization (P-trend=0.01)					
	SAG	37.0%	Ref		
	MAG	32.1%	0.82	[0.69;0.96]	0.02
	TAG	31.4%	0.71	[0.53;0.94]	0.02

SAG single arterial graft, MAG multiple arterial graft, TAG total arterial graft. MI, myocardial infarction.

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

		10-year mortality				10-year MACE		
Variable	Units	HR	CI.95	p-value		HR	CI.95	p-value
TAG index	≤1/3	Ref				Ref		
	1/3-2/3	0.85	[0.70;1.04]	0.11		0.84	[0.72;0.99]	0.03
	>2/3	0.73	[0.57;0.93]	0.01		0.75	[0.62;0.92]	0.004
	Continuous	0.68	[0.47;0.97]	0.03		0.68	[0.51;0.90]	0.007
Age		1.07	[1.06;1.08]	< 0.001		1.03	[1.02;1.04]	< 0.001
Non-Caucasian		0.72	[0.46;1.11]	0.13		0.76	[0.56;1.04]	0.08266
Female		0.96	[0.74;1.24]	0.73		1.17	[0.96;1.44]	0.11558
NYHA functional class		1.11	[0.90;1.38]	0.33		1.15	[0.97;1.37]	0.10295
DM		1.33	[1.10;1.61]	0.004		1.15	[0.98;1.35]	0.07996
COPD		1.14	[0.72;1.80]	0.57		1.09	[0.73;1.62]	0.67814
Asthma		1.32	[0.90;1.92]	0.15		1.64	[1.23;2.19]	< 0.001
Creatinine		1.01	[1.00;1.01]	< 0.001		1.00	[1.00;1.01]	0.03723
LVEF		1.76	[1.46;2.12]	< 0.001		1.28	[1.09;1.50]	0.00232
PVD		1.35	[1.02;1.80]	0.04		1.39	[1.09;1.77]	0.00715
AF		2.14	[1.35;3.39]	0.001		1.71	[1.10;2.66]	0.01710
MI		1.09	[0.91;1.30]	0.35		1.08	[0.93;1.24]	0.31520
CVD		1.49	[1.01;2.19]	0.04		1.35	[0.96;1.90]	0.08392
Hypertension		1.22	[0.96;1.54]	0.10		1.16	[0.97;1.39]	0.11294
Hyperlipidaemia		0.94	[0.66;1.34]	0.73		0.86	[0.65;1.13]	0.27583
RCA		1.08	[0.85;1.35]	0.54		1.04	[0.87;1.25]	0.66037
Off-pump		1.08	[0.90;1.30]	0.41		1.00	[0.86;1.17]	0.96181

MACE major adverse cardiac events, 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, EA endarterectomy.

Supplementary Table 1. Graft configuration

Group	SAG	MAG			TAG		
Total n	1084	1010			390		
Graft Conf	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.

Supplementary Table 2. Standardised mean difference between individual group comparison before and after IPTW.

	Unmatched average	Unmatched SAGvsMAG	Unmatched SAGvsMAG	Unmatched MAGvsTAG	Weighted average	Weighted SAGvsMAG	Weighted SAGvsTAG	Weighted MAGvsTAG
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
Non-caucasian	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
Hyperlipidaemia	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

Table 1 SAG single arterial graft, MAG multiple arterial graft, TAG total arterial graft. IPTW inverse probability of treatment weighting. DM diabetes mellitus, COPD chronic obstructive pulmonary disease, LVEF left ventricle ejection fraction, PVD peripheral vascular disease, AF atrial fibrillation, MI myocardial infarction, VQ vessel quality, RCA right coronary artery, NYHA New York Heart Association, CVA cerebrovascular disease.

Supplementary Table 3. Multivariable Cox model stratified by number of grafts

		10-year mortality				10-year MACE		
Variable	Units	HR	CI.95	p-value		HR	CI.95	p-value
group *†	SAG	Ref				Ref		
	MAG	0.86	[0.71;1.04]	0.12		0.83	[0.71;0.97]	0.01
	TAG	0.77	[0.58;0.97]	0.04		0.78	[0.63;0.97]	0.02
Age		1.07	[1.06;1.08]	< 0.001		1.03	[1.02;1.04]	< 0.001
Non-caucasian		0.73	[0.47;1.13]	0.16		0.77	[0.57;1.05]	0.10
Female		0.93	[0.72;1.20]	0.57		1.15	[0.94;1.41]	0.17
NYHA functional class		1.10	[0.89;1.36]	0.40		1.15	[0.97;1.36]	0.11
DM		1.33	[1.10;1.62]	0.003		1.15	[0.98;1.35]	0.08
COPD		1.16	[0.74;1.84]	0.51		1.08	[0.73;1.61]	0.69
Asthma		1.31	[0.90;1.92]	0.16		1.66	[1.25;2.22]	< 0.001
Creatinine		1.01	[1.00;1.01]	< 0.001		1.00	[1.00;1.01]	0.034
LVEF		1.76	[1.46;2.12]	< 0.001		1.28	[1.09;1.50]	0.002
PVD		1.38	[1.03;1.83]	0.03		1.40	[1.10;1.78]	0.006
AF pre		2.20	[1.39;3.48]	< 0.001		1.74	[1.12;2.71]	0.01
MI		1.09	[0.91;1.31]	0.33		1.08	[0.93;1.25]	0.30
CVD		1.52	[1.03;2.24]	0.03		1.37	[0.98;1.93]	0.07
Hypertension		1.21	[0.96;1.53]	0.10		1.16	[0.96;1.38]	0.12
Hyperlipidemia		0.96	[0.67;1.37]	0.80		0.87	[0.66;1.15]	0.32
RCA		1.13	[0.90;1.43]	0.30		1.08	[0.89;1.30]	0.44
Off-pump		1.09	[0.91;1.32]	0.35		1.01	[0.87;1.17]	0.90

SAG single arterial graft, MAG multiple arterial graft, TAG total arterial graft. MACE major adverse cardiac events, 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, EA endarterectomy.

**P-value for test for trend=0.03 for mortality.*

†P-value for test for trend=0.006 for MACE

Supplementary Table 4. Compliance to goal directed medical therapy in the three 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%

Supplementary Table 5. Comparison of cardiac vs non-cardia cause of death in the three groups.

	SAG	MAG	TAG	P value
N (%)	1084	941	843	
Cardiovascular death	91 (8.4)	74 (7.8)	55 (6.5)	0.220
Non cardiovascular death	165 (15.2)	118 (12.5)	95 (11.3)	

Supplementary Table 6. 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)	0.60

Supplementary Table 7. Treatment effect estimation in patient older than 70 years old

		10-y cumulative incidence	Hazard Ratio	CI.95	p-value
All-cause death (P-trend=0.15)					
	SAG	41.7%	Ref		
	MAG	37.8%	0.91	[0.66;1.25]	0.55
	TAG	29.3%	0.67	[0.39;1.17]	0.16
Death/MI/STROKE/revascularization (P-trend=0.09)					
	SAG	51.3%	Ref		
	MAG	47%	0.95	[0.72;1.25]	0.70
	TAG	42.3%	0.65	[0.40;1.07]	0.09

SAG single arterial graft, MAG multiple arterial graft, TAG total arterial graft. MI, myocardial infarction.

Supplementary Table 8. Treatment effect estimation in insulin-dependent diabetic patients.

		10-y cumulative incidence	Hazard Ratio	CI.95	p-value
All-cause death (P-trend=0.02)					
	SAG	24.6%	Ref		
	MAG	21.1%	0.84	[0.69;1.03]	0.10
	TAG	18.4%	0.68	[0.48;0.96]	0.03
Death/MI/STROKE/revascularization (P-trend=0.007)					
	SAG	37.0%	Ref		
	MAG	32.1%	0.82	[0.69;0.96]	0.02
	TAG	31.4%	0.71	[0.53;0.94]	0.02

SAG single arterial graft, MAG multiple arterial graft, TAG total arterial graft. MI, myocardial infarction.

Supplementary Table 9. Treatment effect estimation of MAG/TAG group vs SAG according to multivariable model and without propensity score.

		10-y cumulative incidence	HazardRatio	CI.95	p-value
All-cause death					
	SAG	24.6%	Ref		
	MAG/TAG	19.5%	0.78	[0.65;0.92]	0.004
MI					
	SAG	5.5%	Ref		
	MAG/TAG	4.9%	0.85	[0.59;1.22]	0.38
Revascularization					
	SAG	11.3%	Ref		
	MAG/TAG	10.8%	0.91	[0.71;1.18]	0.49
STROKE					
	SAG	5.6%	Ref		
	MAG/TAG	4.2%	0.73	[0.50;1.07]	0.10
Death/MI/STROKE/revascularization					
	SAG	37.0%	Ref		
	MAG/TAG	30.8%	0.79	[0.68;0.90]	<0.001

SAG single arterial graft, MAG multiple arterial graft, TAG total arterial graft. MI, myocardial infarction

Supplementary Table 10. Treatment effect estimation in the overall population without adjustment.

		10-y cumulative incidence	HazardRatio	CI.95	p-value
All-cause death (P-trend=0.003)					
	SAG	24.6%	Ref		
	MAG	20.2%	0.80	[0.67;0.97]	0.02
	TAG	17.9%	0.71	[0.54;0.93]	0.01
MI (P-trend=0.33)					
	SAG	5.5%	Ref		
	MAG	5.0%	0.88	[0.60;1.30]	0.53
	TAG	4.6%	0.77	[0.44;1.35]	0.37
Revascularization (P=0.35)					
	SAG	11.3%	Ref		
	MAG	11.1%	0.95	[0.72;1.24]	0.70
	TAG	9.9%	0.83	[0.56;1.21]	0.33
STROKE (P-trend=0.09)					
	SAG	5.6%	Ref		
	MAG	4.3%	0.76	[0.51;1.15]	0.20
	TAG	3.7%	0.64	[0.35;1.18]	0.15
Death/MI/STROKE/revascularization (P-trend=0.001)					
	SAG	37.0%	Ref		
	MAG	31.1%	0.80	[0.68;0.92]	0.003
	TAG	30.2%	0.76	[0.62;0.94]	0.01

SAG single arterial graft, MAG multiple arterial graft, TAG total arterial graft. MI, myocardial infarction.

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.

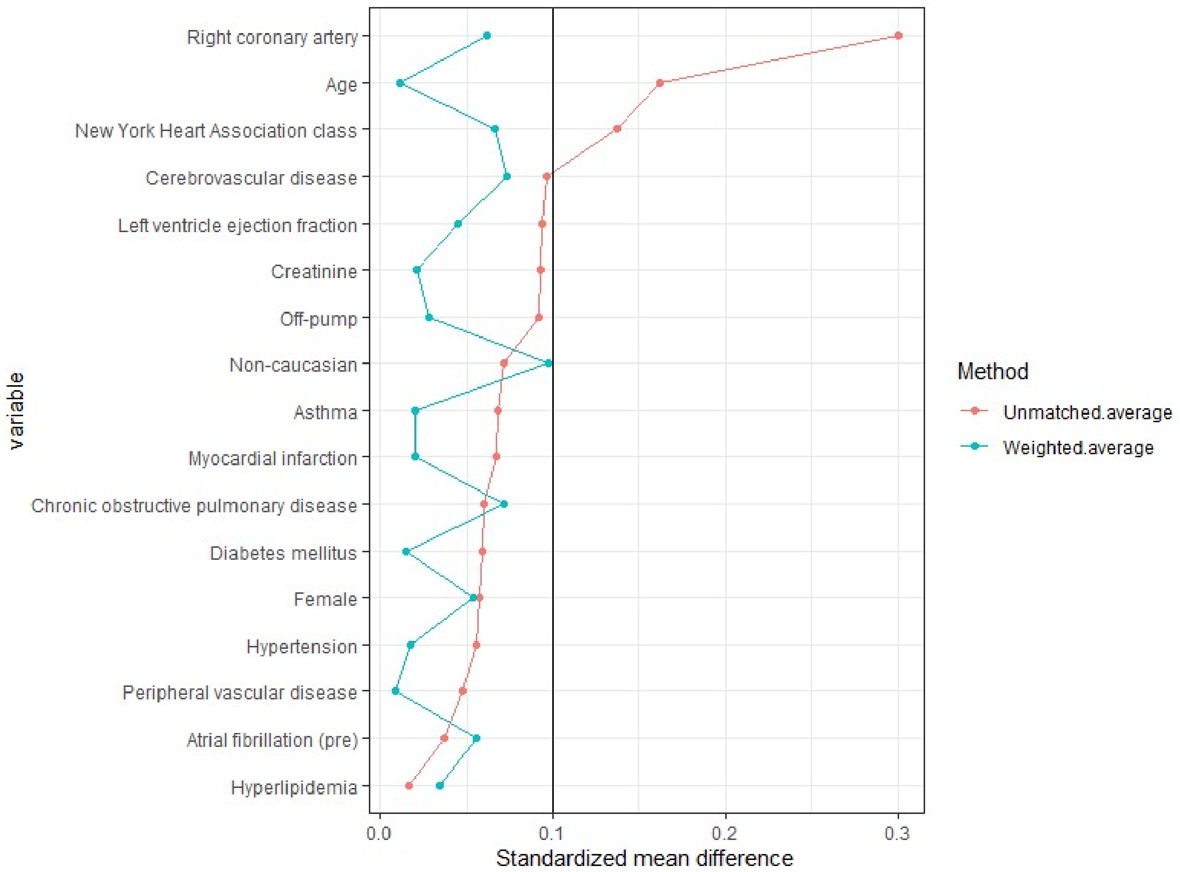


Figure 2A. Kaplan-Meier curves showing cumulative 10-year mortality in the three groups after inverse probability of treatment weighting (IPTW). The confidence limit of each curve is shown as shaded area. SAG single arterial graft, MAG multiple arterial graft, TAG total arterial graft.

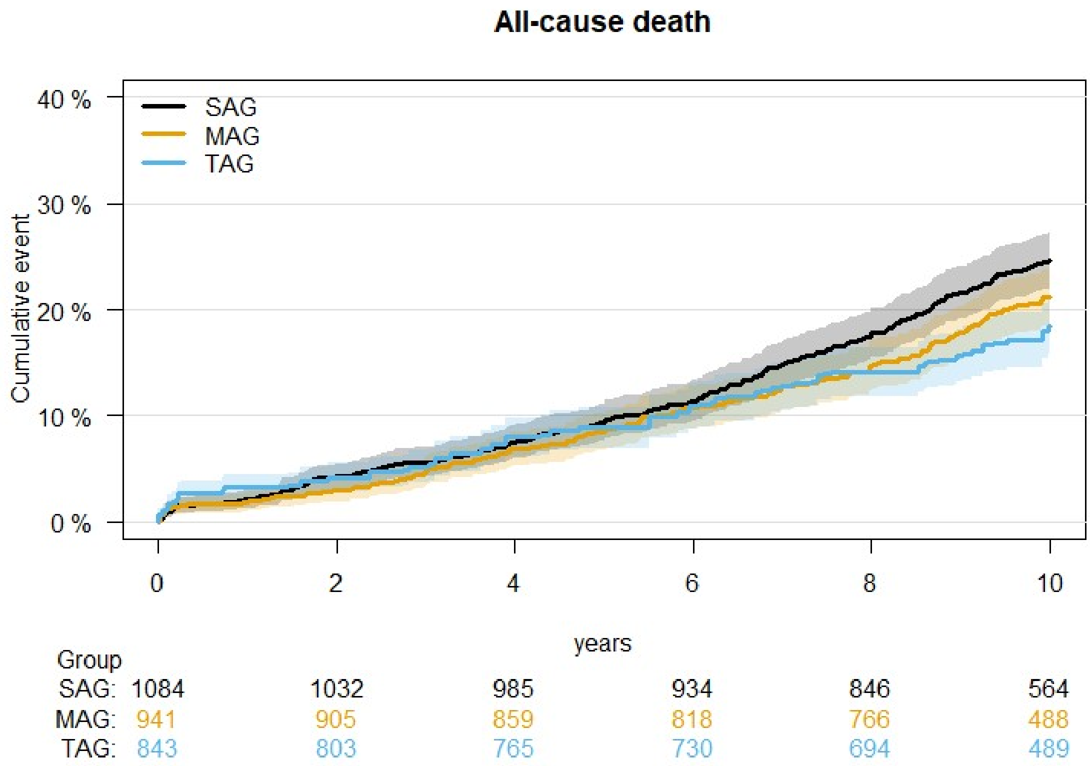


Figure 2B. Kaplan-Meier curves show cumulative 10-year incidence of composite of death, MI, stroke and repeat revascularization in the three groups after inverse probability of treatment weighting (IPTW). The confidence limit of each curve is shown as shaded area. SAG single arterial graft, MAG multiple arterial graft, TAG total arterial graft.

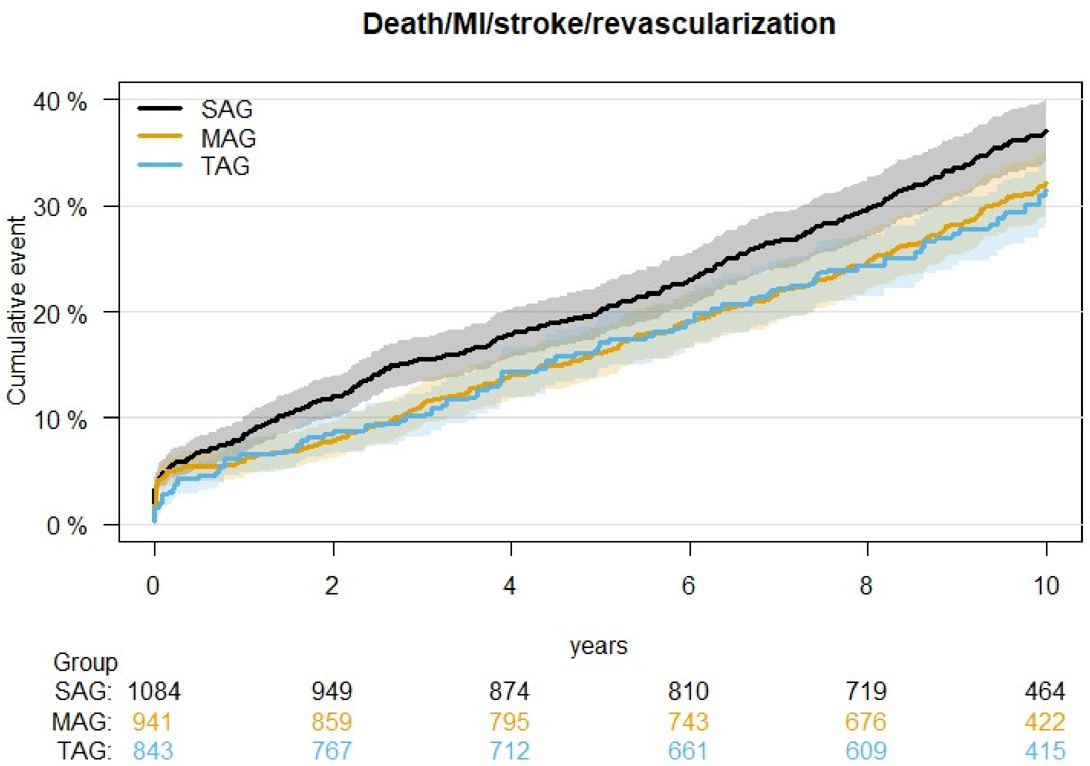


Figure 3A. Linear relationship between the TAG index and the risk of 10-year mortality. TAG index median (0.5) as reference.

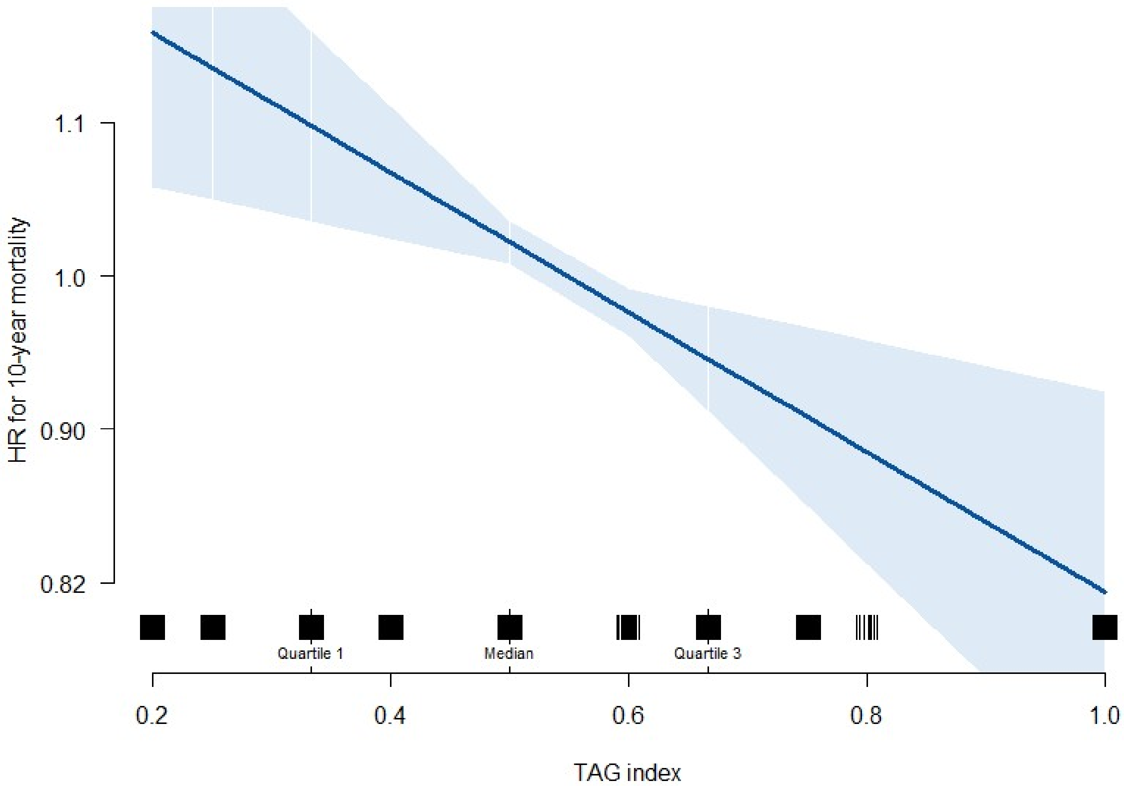
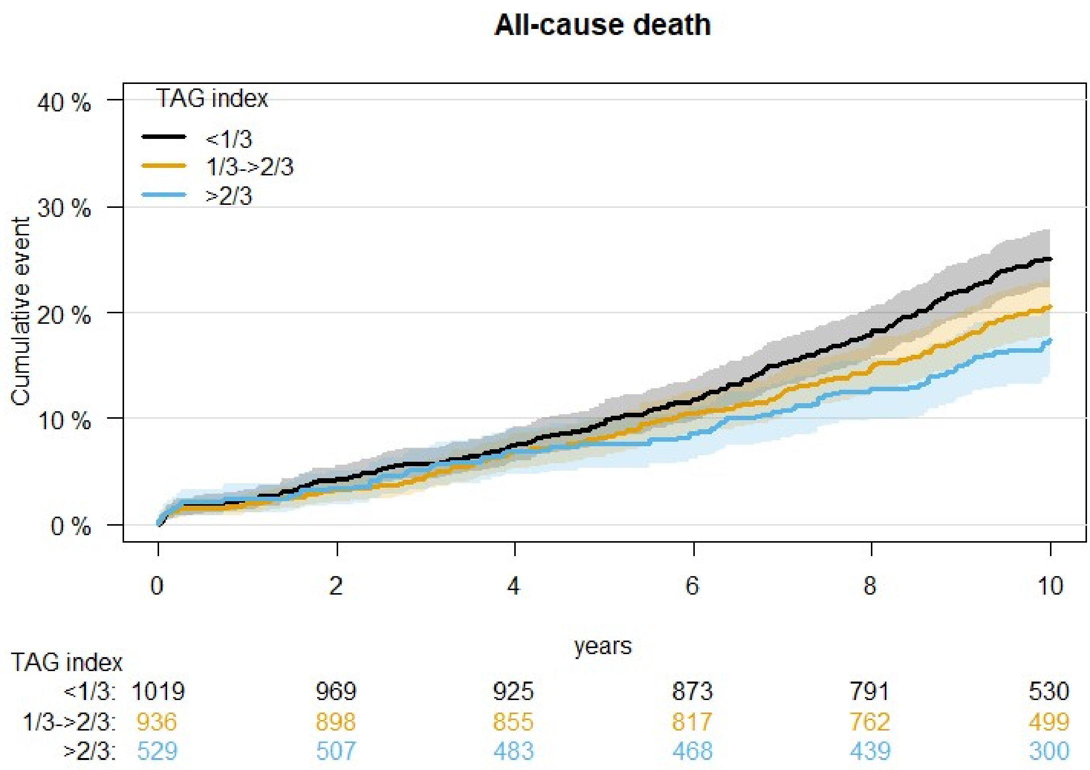


Figure 3B. Kaplan-Meier curve show cumulative 10-year mortality according to the TAG index. The confidence limit of each curve is shown as shaded area.



Supplementary Figure 1. Standardized mean difference before and after inverse probability of treatment weighting for each comparison (1: single arterial graft (SAG), 2: multiple arterial graft (MAG); 3: total arterial graft (TAG)).