Long-Term Survival After CABG with Multiple Versus Single Arterial Grafts in The Randomized SYNTAX Trial

Daniel J.F.M. Thuijs*, Piroze Davierwala*, Milan Milojevic, Salil V. Deo, Thilo Noack, A. Pieter Kappetein, Patrick W. Serruys, Friedrich-Wilhelm Mohr, Marie-Claude Morice, Michael J. Mack, L. Elisabeth G.E. Ståhle, Niels J. Verberkmoes, David R. Holmes Jr., Stuart J. Head, for the SYNTAX Extended Survival Investigators

** both authors contributed equally*

Submitted

ABSTRACT

Objectives

To evaluate the impact coronary artery bypass grafting (CABG) using multiple versus single arterial grafts (MAG versus SAG) on long-term survival in the SYNTAX trial.

Methods

The present analysis included the randomized and registry as-treated CABG patients (n=1509) from the SYNTAX Extended Survival study (SYNTAXES). Patients with only venous (n=42) or synthetic grafts (n=1) were excluded. The primary endpoint was all-cause death at maximum follow-up. Multi-variable Cox regression was used to adjust for differences in baseline characteristics. Sensitivity analysis using propensity matching with inverse probability for treatment weights (IPTW) was performed.

Results

Of the 1466 included patients, 465 (31.7%) received MAG and 1001 (68.3%) SAG. Patients receiving MAG were younger and at lower risk. At maximum follow-up of 12.6 years, all-cause death occurred in 23.6% of MAG and 40.0% of SAG patients (adjusted hazard ratio (HR) 0.58, 95% confidence interval (CI) [0.46-0.72], P=0.001), which was confirmed by sensitivity analysis. MAG in patients with three-vessel disease was associated with significant lower unadjusted and adjusted all-cause death at 12.6 years (adjusted HR 0.65, 95%CI [0.44-0.97], P=0.033), whereas no significance was observed following after risk-adjustment in patients with left main disease, with and without diabetes, and among SYNTAX-score tertiles.

Conclusions

In the present analysis of all-comers patients from the SYNTAX trial, MAG resulted in markedly lower all-cause death at 12.6-year follow-up, compared to a SAG strategy. Hence, the striking long-term survival benefit of MAG over SAG in the SYNTAX trial encourages a more extensive use of multiple arterial grafting.

Keywords

SYNTAX; coronary artery disease; revascularisation CABG; multiple arterial grafts; survival

INTRODUCTION

Whether coronary artery bypass grafting (CABG) should be performed with multiple arterial grafts (MAG) in patients requiring bypass surgery remains fiercely debated. Observational studies identified the long-term advantages of multiple arterial grafting compared with the use of a single arterial graft (SAG).[1-5] However, the randomized Arterial Revascularization Trial ART trial failed to show superiority of CABG with a bilateral- versus a single internal mammary artery (BITA versus SITA) in the intention-to-treat analysis. The as-treated analysis, however, showed that multiple arterial grafting resulted in a significant decrease in all-cause death (18.6%) compared with the use of a single arterial graft (23.1%; HR 0.81, 95% CI [0.68-0.95]).[6] Besides, at a 10 year follow-up, the overall patency for venous bypass grafts is considerably lower than that for arterial bypass grafts. (61% vs. 85%, respectively).[7] Therefore, assessment of all-cause death after MAG versus SAG beyond 10-year follow-up is required to adequately support the clinical utility of a multiple arterial grafting strategy in daily CABG practice. The present pre-specified sub-analysis of the SYNTAX Extended Survival study [8] aimed to evaluate the impact of multiple arterial grafts versus a single arterial graft on long-term survival (>10 years) in patients with complex coronary artery disease (CAD).

METHODS

Study design

The rationale, design and outcomes of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (NCT00114972) have been reported previously.9-13 In brief, the SYNTAX trial randomized patients with de novo three-vessel disease (3VD) and/or left main coronary artery disease (LMCAD) to undergo either percutaneous coronary intervention (PCI) with paclitaxel-eluting stents or CABG. Patients who were ineligible for randomization were included in parallel nested registries for PCI-ineligible patients (CABG registry n=1077) and CABG-ineligible patients (PCI-registry n=198). Out of the 1077 patients in the CABG registry, 649 were randomly allocated for a long-term follow-up, of which 644 underwent CABG (as-treated).

The present analysis is a sub-study of the SYNTAX Extended Survival study (NCT03417050) and included patients from the randomized and registry cohorts of the SYNTAX trial that underwent CABG.[8] Patients who received only venous or synthetic grafts were excluded. Follow-up was performed in accordance with local law and regulations of each participating institution and complied with the Declaration of Helsinki. The extended follow-up of the SYNTAXES study was funded by the German Heart Research Foundation (GHF; Frankfurt am Main, Germany). The sponsor had neither a role in the study design nor in the collection, analyses and interpretation of the study data, nor in the decision to publish.

Endpoints and definitions

The primary endpoint of the current study was all-cause death in patients who underwent CABG with multiple versus single arterial grafts (as-treated MAG versus SAG). Furthermore, the primary endpoint was examined in pre-specified subgroups of patients (i) with three-vessel disease, (ii) LMCAD (iii) patients with medically treated diabetes and (iv) those without diabetes, and (v) according to SYNTAX score tertiles (low: 0-22, intermediate 23-32, high≥33).

The MAG cohort consisted of patients who received two or more arterial grafts, irrespective of configuration or type of graft (internal thoracic arteries, radial artery or gastroepiploic artery). The SAG cohort consisted of patients with only one single arterial graft. LMCAD was defined as patients having any left main disease, either isolated, or with single-vessel, two-vessel or three-vessel CAD. Three-vessel disease was defined as patients with CAD involving all three vessels, in the absence of LMCAD.[9, 12] Coronary disease anatomical complexity was reported according to the SYNTAX score, with higher SYNTAX scores indicating more complex CAD.[14] SYNTAX score subgroups were defined according to the classical tertiles; low ≤22, intermediate 23-32 and high ≥33.[10, 15] The European System for Cardiac Operative Risk Evaluation (EuroSCORE) was used to predict operative risk. Diabetes was defined as those patients requiring treatment with oral hypoglycemic agents and/or insulin. Incomplete revascularisation was determined post-procedurally by correlating all lesions requiring bypass, identified during the preoperative Heart Team meeting, to those lesions that were revascularized during the procedure.

Coronary artery bypass grafting techniques

Bypass surgery was performed with the aim to achieve complete revascularisation of all vessels with a diameter ≥ 1.5 mm or larger and with an angiographic diameter stenosis of ≥ 50% as quantified on coronary angiography and discussed during preoperative Heart Team meetings. The choice and configuration of bypass grafts, as well as the surgical technique utilized, was left at the discretion of the individual surgeon.

Statistical analyses

The current analysis was performed according to the as-treated principle. Discrete variables were expressed as percentages with frequencies, and were compared by Chi-square tests or Fisher's exact test when the expected frequency in any cell was less than 5. Continuous variables were summarized as mean ± standard deviation (SD) and were compared by independent samples t-test, if normally distributed, or the Wilcoxon rank-sum test if non-normally distributed. Unadjusted cumulative all-cause death rates were estimated according to the Kaplan–Meier method and the difference between the use of MAG and SAG was evaluated with a log-rank test. Kaplan Meier survival curves are truncated at a time-point in follow-up, when at least 10% of patients were still at risk, to avoid visual misinterpretation.[16] Exploratory analyses were performed for bilateral versus single internal thoracic artery (BITA vs SITA) and total arterial revascularisation (TAR) versus without TAR. Survival analyses for the use of MAG versus SAG were adjusted using multivariable Cox regression analysis that included the following combination of clinically and statistically relevant preoperative variables[17]: age (as a continuous variable; per 1 year increase), sex, body mass index ≥ 30kg/m^2 , medically treated hypertension, medically treated hyperlipidemia, history of myocardial infarction (MI), unstable angina, history of stroke and/or transient ischemic attack, medically treated diabetes mellitus, peripheral vascular disease, carotid artery disease, Creatinine >200 micromole per liter, chronic obstructive pulmonary disease, left ventricular ejection fraction<50%, presence/absence of LMCAD, and SYNTAX score (as a continuous variable). To further confirm results obtained with the multi-variable Cox model, a sensitivity analysis was performed using propensity score derived weighing. Hence, the same preoperative covariates were included in a mixed model to develop a propensity score for each patient to receive MAG rather than SAG. Volume differences between MAG vs SAG among 85 centers included in the original SYNTAX study were corrected for by including this as a random effect term in the mixed model. From the propensity scores, truncated Inverse Probability Treatment Weighting (IPTW) weights (limited to 1st and 99th percentile) were calculated and included to fit a weighed Cox proportional hazards model for all-cause mortality. More information regarding the statistical methods and relevent results are presented in the Supplementary Materials. Finally, adjusted survival analyses in the pre-specified subgroups between the use of MAG versus SAG were performed by multivariable Cox regression analysis adjusting for the same preoperative variables mentioned above. Statistical tests were reported as 2-sided, and a $P<0.05$ was considered as statistically significant. Statistical analyses were performed with SPSS Statistics software, version 24 (IBM Corporation, Armonk, NY, USA) and R (The R Foundation for Statistical Computing, Austria).

RESULTS

Patient-flow and characteristics

The as-treated CABG cohort consisted of 1466 patients, with 465 in the MAG and 1001 the SAG group (Figure 1). Information on vital status of patients at the 10-year follow-up mark was available in 94% of all included patients. The mean age of patients who received MAG was 62.3 years versus 66.5 years in patients who received SAG (P<0.001, Table 1). Patients receiving MAG were less likely to be female and had a lower cardiovascular risk-profile. Approximately a quarter of patients had diabetes. The mean EuroSCORE was 2.9 versus 4.4 (P<0.001) and the mean SYNTAX score was 32.2 versus 33.3 (P=0.14), among MAG versus SAG patient, respectively.

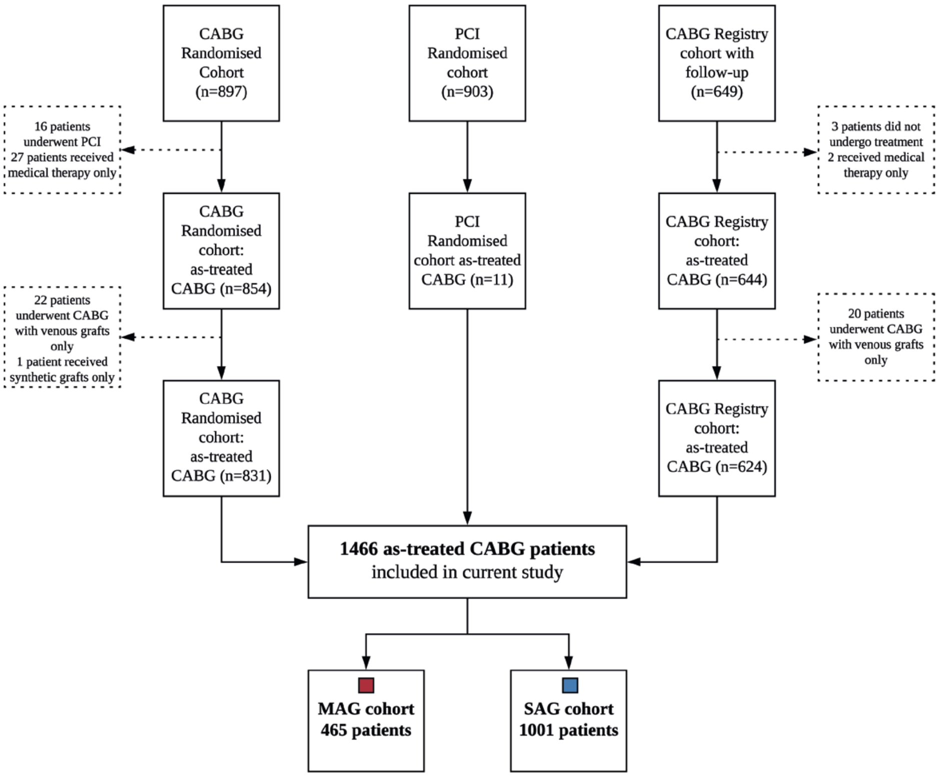


Figure 1. Flow of as-treated CABG patients through the SYNTAX trial.
Abbreviations used: CABG; coronary artery bypass grafting, MAG; multiple arterial grafting, PCI; percutaneous coronary intervention, SAG; single arterial grafting.

Table 1. Baseline demographic and clinical characteristics of patients undergoing CABG in the SYNTAX trial.

Characteristics	CABG (n = 1466)[#]		
	MAG (N=465)	SAG (N=1001)	P-value
Age (years)	62.3 ± 9.7	66.5 ± 9.2	<0.0001
Female sex – no. (%)	64 (13.8)	224 (22.4)	<0.0001
Body mass index ≥30 (kg/m^2) – no (%)	144 (31.0)	310/1000 (31.0)	0.99
Medically Treated Diabetes – no. (%)			
Oral medication or insulin	103 (22.2)	259 (25.9)	0.12
Insulin	38 (8.3)	102 (10.2)	0.22
History of nicotine abuse – no. (%)	319/462 (69.0)	657/994 (66.1)	0.27
History of Chronic Obstructive Pulmonary Disease – no. (%)	34 (7.3)	89 (8.9)	0.31
Carotid Artery disease – no. (%)	45 (9.7)	101 (10.1)	0.81
Peripheral Vascular Disease – no. (%)	49 (10.5)	128 (12.8)	0.22
Creatinine >200 micromol/L	6 (1.3)	21 (2.1)	0.29
History of myocardial infarction – no. (%)	128/457 (28.0)	351/984 (35.7)	0.004
History of stroke or TIA– no. (%)	39/464 (8.4)	94/996 (9.4)	0.52
Medically Treated Hypertension (≥130/85mmHg) – no. (%)	344/459 (74.9)	742/990 (74.9)	>0.99
Medically Treated Hyperlipidemia – no. (%)	361/459 (78.6)	751/985 (76.2)	0.31
Angina – no. (%)			
Stable	265 (57.0)	610 (60.9)	0.15
Unstable	119 (25.6)	256 (25.6)	0.99
Impaired Left Ventricular Ejection Fraction (<50%) – no. (%)[Ω]	74 (15.9)	265/996 (26.6)	<0.0001
EuroSCORE value – mean ± SD	2.9 ± 2.9	4.4 ± 4.9	<0.0001
SYNTAX score[*] – mean ± SD	32.2 ± 12.8	33.3 ± 13.0	0.14
No. of lesions[*] – mean ± SD	4.3 ± 1.7	4.4 ± 1.8	0.80
Left main[∞], any	181 (38.9)	445 (44.5)	0.046
Three-vessel[∞], without left main involvement	284 (61.1)	556 (55.5)	0.046

Values are shown as mean ± SD (standard deviation) or frequencies in percentages and (n), unless otherwise noted. [#]Data is reported according the as-treated principle based on the randomized and registry as-treated CABG patients. Ω Impaired left ventricular ejection fraction (LVEF) was defined as < 50%. [*]core laboratory assessment, [∞]site reported. Abbreviations used: MAG: multiple arterial grafts, SAG: single arterial graft, CABG; coronary artery bypass grafting, BMI: body mass index, TIA: transient ischemic attack.

Off-pump surgery was performed in 101 patients (21.7%) who underwent CABG with MAG versus 146 patients (14.5%) who received SAG (Table 2). Both MAG and SAG patients received an average of 2.8 conduits per patients, with 3.4 distal anastomoses per patient. BITA grafting was performed in 341 patients (73.3) who received MAG. In the SAG cohort, 995 patients (99.4%) received a single left internal thoracic artery (LITA), 2 patients a radial artery (0.2%) and 4 patients (0.4%) a single right internal thoracic artery (RITA), in addition to venous grafts. The rate of complete revascularisation was similar among patients receiving MAG (68.0%) versus SAG (69.4%).

Table 2. Surgical characteristics.

Characteristic	MAG (N = 465)	SAG (N = 1001)	P-value
Average number of conduits per patient	2.8 ± 0.7	2.8 ± 0.8	0.74
Average number of distal anastomoses per patient	3.4 ± 0.9	3.4 ± 1.0	0.75
Off-pump CABG	101 (21.7)	146 (14.5)	0.003
Grafts used*:		*	
LITA	463 (99.6)	995 (99.4)	0.68
LITA/RITA	341 (73.3)	0 (0)	<0.0001
Radial artery	192 (41.3)	2 (0.2)	<0.0001
Gastroepiploic Artery	1 (0.2)	0 (0)	0.14
Venous	245 (52.7)	985 (98.4)	<0.0001
Arterial graft to LAD	461 (99.8)	977 (98.0)	0.008
Complete revascularisation	316 (68.0)	695 (69.4)	0.57

Values are shown as mean ± SD (standard deviation) or frequencies in percentages and (n), unless otherwise noted. "*Four patients received a single right internal thoracic artery (RITA), in addition to venous graft(s) in the "single" cohort. Abbreviations used: MAG: multiple arterial grafts, SAG: single arterial graft, CABG: coronary artery bypass grafting, LAD: left anterior descending artery, LITA: left internal thoracic artery, RITA: right internal thoracic artery.

Clinical outcomes

At 12.6 years of follow-up, all-cause death occurred in 23.6% of patients who received MAG versus 40.0% of those undergoing CABG with SAG (unadjusted HR 0.65, 95% CI [0.51-0.83], P<0.001, Figure 2, graphical abstract). After correcting for preselected baseline variables, MAG remained to be associated with a significant lower all-cause death rate as compared with those undergoing CABG with SAG (adjusted HR 0.74 (95% CI [0.55-0.98], P=0.038, Table 3).

CABG with MAG was associated with lower unadjusted all-cause death rates in pre-specified subgroups of patients with 3VD and LMCAD (unadjusted HR 0.56, 95% CI [0.41-0.75]; and HR 0.60, 95% CI [0.43-0.85], respectively, P for interaction=0.73) (Figure 3A, 3B, Table 3). Furthermore, the use of MAG provided an unadjusted survival benefit in subgroups of patients with diabetes, without diabetes (Figure 3C, 3D) and in those with the least and most complex CAD (as reflected by low and high SYNTAX scores, Figure 4A-4C), compared with SAG. After multivariable adjustment the 12.6-year survival benefit of MAG over SAG remained significant in patients with 3VD (adjusted HR 0.65, 95% CI [0.44-0.97], P=0.033, Table 3), while a numerical and non-significant difference was found after adjustment in subgroup of patients with LMCAD, with and without diabetes and according to CAD complexity defined by SYNTAX score tertiles. The IPTW sensitivity analysis confirmed that MAG was associated with lower mortality [(HR 0.75, 95% CI [0.57 - 0.99], P = 0.04]; Supplemental Materials, Figure S1-S2).

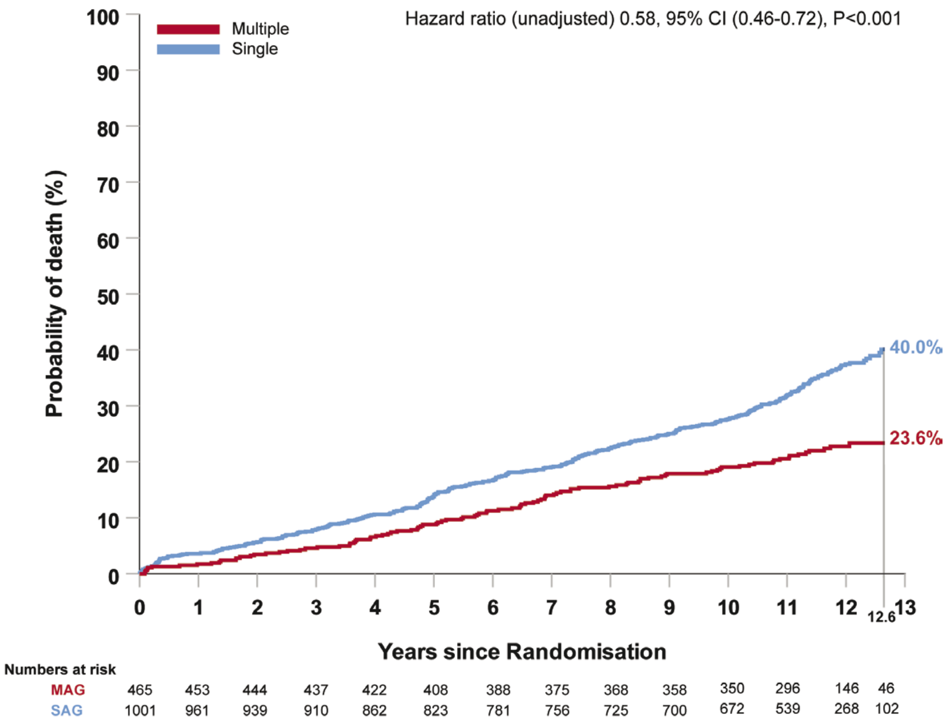


Figure 2. All-cause death of patients who underwent CABG with single versus multiple arterial grafts. Kaplan-Meier curves describing the probability of death up to 12.6 years follow-up in the overall cohort of patients who underwent CABG with multiple arterial grafts (MAG; red curve) versus single (SAG; blue curve) revascularisation

Abbreviations used: HR; hazard ratio, CI; confidence interval, MAG; multiple arterial grafts, SAG; single arterial graft.

Exploratory analyses showed that CABG using bilateral internal thoracic arteries versus a single internal thoracic artery was associated with a lower rate of all-cause death at 12.6 years (BITA: 21.8% vs SITA: 40.3%; unadjusted HR 0.54, 95%CI [0.42-0.70], P<0.001 and adjusted HR 0.72, 95%CI [0.52-1.01], P=0.054, Supplementary Materials Figure S3). Of those that received SITA, only 2 patients received an additional radial artery graft (0.2%), whereas it was used in 73 patients (21.4%) undergoing BITA grafting. Total arterial revascularisation (TAR), compared with no-TAR, was associated with a significant unadjusted lower all-cause death rate at 12.6 years follow-up (unadjusted HR 0.70, 95%CI [0.55-0.93P=0.015, Supplementary Materials Figure S4). Of note, 245 patients from the no-TAR cohort underwent CABG with multiple arterial grafts. After multivariable adjustment the difference in favor of total arterial revascularisation was no longer statistically significant (adjusted HR 0.80, 95%CI [0.55-1.16], P=0.24).

Table 3. Multivariable Cox Regression model: unadjusted and adjusted outcomes (as-treated).

Cohort	MAG 12.6-year deaths (%)	SAG 12.6-year deaths (%)	Unadjusted Hazard Ratio (95% CI), P-value	*P* for interaction	Adjusted Hazard Ratio (95% CI), P-value
Overall	23.6	40.0	0.58 (0.46-0.72), *P*<0.001	-	0.74 (0.55-0.98), *P*=0.038**
Three-vessel disease	22.5	38.5	0.56 (0.41-0.75), *P*<0.001	0.73	0.65 (0.44-0.97), *P*=0.033
Left main disease	24.9	42.3	0.60 (0.43-0.85), *P*=0.004		0.85 (0.54-1.34), *P*=0.49
Diabetes	39.5	56.7	0.67 (0.46-0.97), *P*=0.036	0.43	0.73 (0.43-1.24), *P*=0.25
No diabetes	19.1	34.6	0.55 (0.42-0.73), *P*<0.001		0.76 (0.54-1.09), *P*=0.14
Coronary complexity					
SYNTAX score 0 – 22	17.5	35.3	0.47 (0.28-0.80), *P*=0.005		0.83 (0.41-1.66), *P*=0.60
SYNTAX score 23-32	28.4	41.7	0.70 (0.48-1.01), *P*=0.060		0.74 (0.44-1.24), *P*=0.25
SYNTAX score ≥ 33	23.6	41.0	0.58 (0.42-0.81), *P*=0.001	0.86	0.71 (0.47-1.09), *P*=0.11

Cox Regression Model on the primary outcome of ten-year all-cause death. Data is reported according the as-treated principle. Ω Impaired left ventricular ejection fraction (LVEF) was defined as < 50%. *core laboratory assessment, ∞site reported. Variables used in the full multivariable Cox regression analysis: age, sex, hypertension, hyperlipidemia, stroke or TIA, diabetes mellitus, peripheral vascular disease, carotid artery disease, chronic obstructive pulmonary disease, creatinine >200micromol/L, left ventricular ejection fraction<50% and SYNTAX score (as a continuous variable). Abbreviations used: MAG: multiple arterial grafts, SAG: single arterial graft, BMI: body mass index (kg/m^2), CABG; coronary artery bypass grafting, COPD: chronic obstructive pulmonary disease, LVEF: left ventricular ejection fraction. **This result was confirmed with a weighted Cox proportional hazards model [HR : 0.75 95% CI (0.57 - 0.99) p = 0.04].

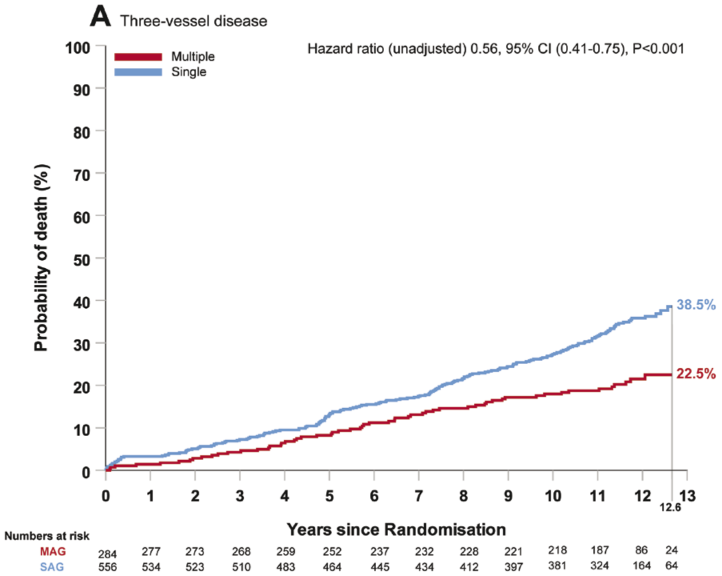


Figure 3. – PANEL A 3VD

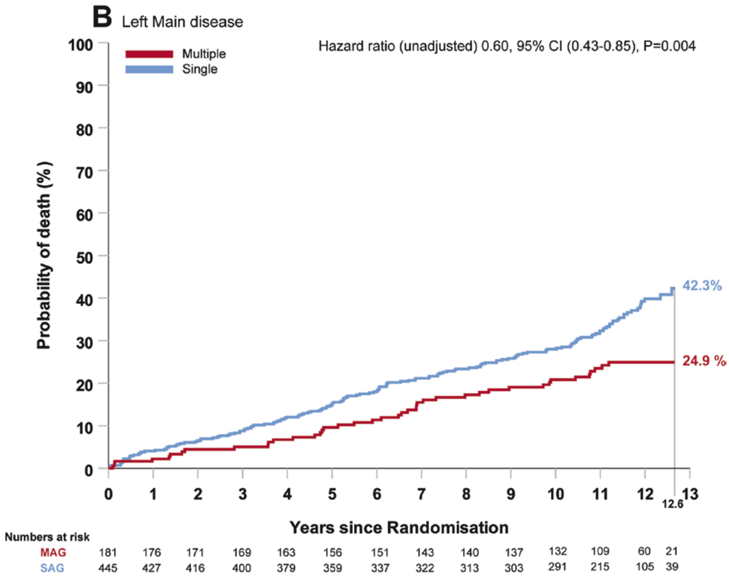


Figure 3. – PANEL B LMCAD

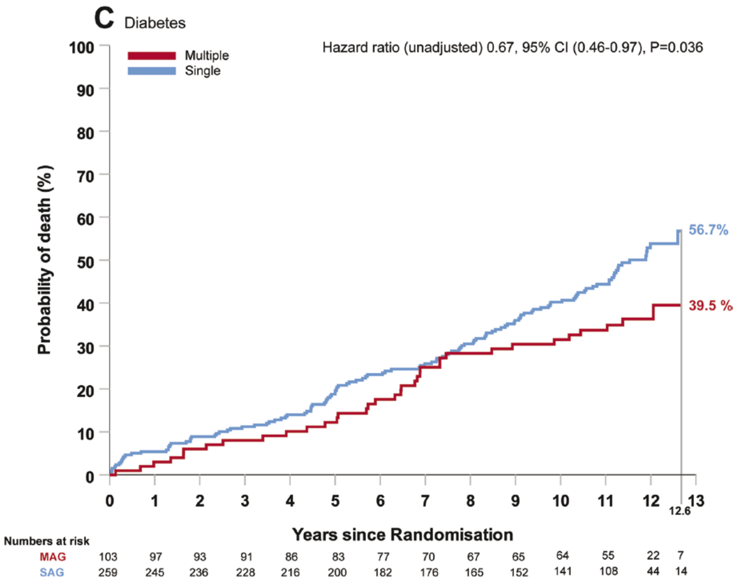


Figure 3. – PANEL C Diabetes

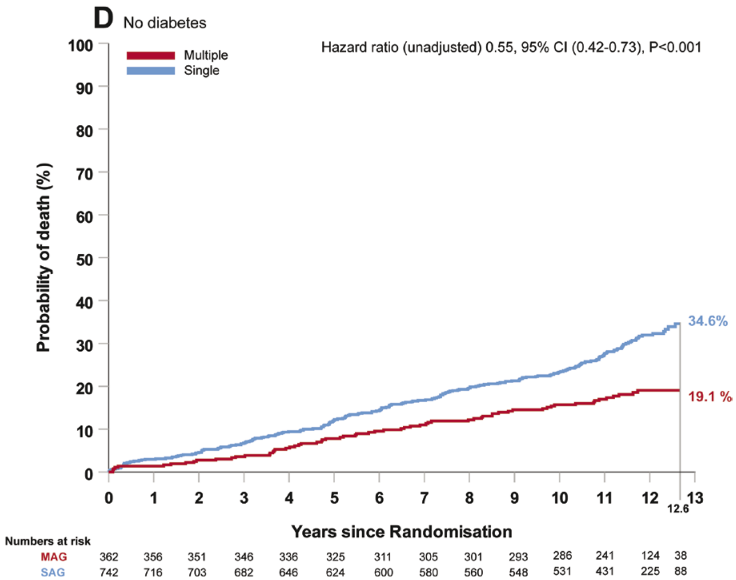


Figure 3. – PANEL D NO Diabetes

All-cause death in patients with three-vessel disease, left main disease, diabetes and no diabetes, who received multiple versus single arterial grafts. Kaplan-Meier curves describing the probability of death up to 12.6 years follow-up in patients with 3VD that underwent CABG and received multiple arterial grafts (MAG; red curve) versus single (SAG; blue curve) (Panel A), those with left main disease (Panel B), medically treated diabetes (Panel C) and those without diabetes (Panel D). The widths of 95% confidence intervals were not adjusted for multiple comparisons, therefore these intervals should not be used for inference about between-group differences. Abbreviations used: HR; hazard ratio, CI; confidence interval, MAG; multiple arterial grafts, SAG; single arterial graft.

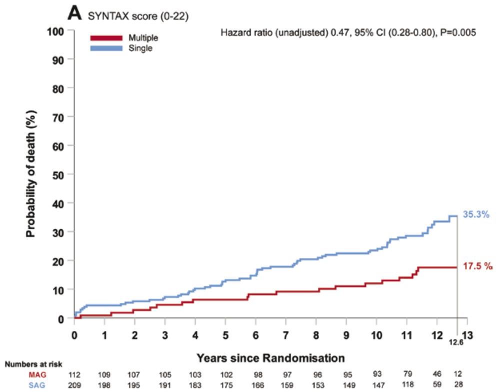


Figure 4. – PANEL A – SYNTAX score 0-22

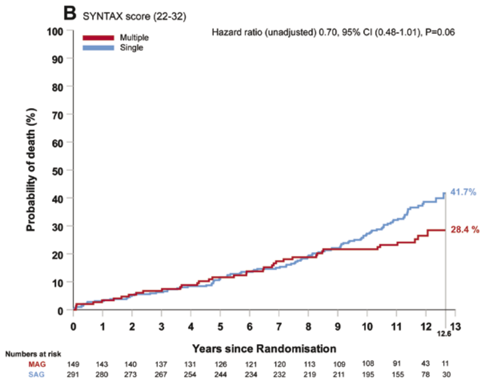


Figure 4. – PANEL B – SYNTAX score 23-32

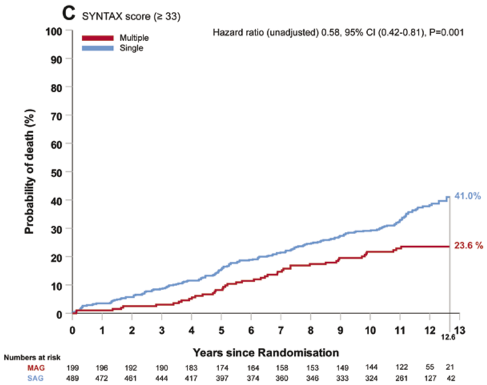
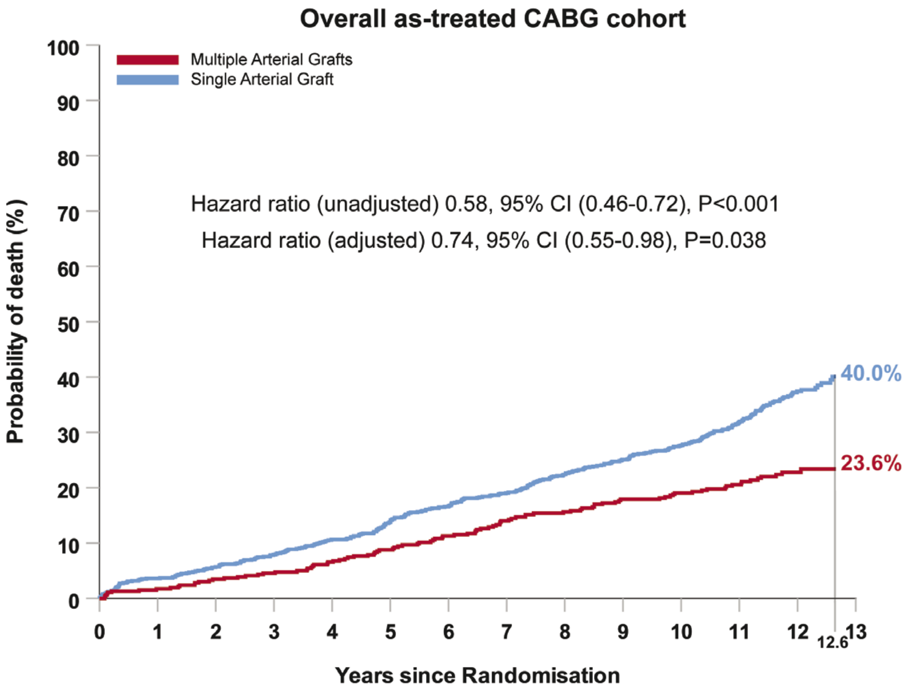


Figure 4. – PANEL C – SYNTAX score ≥33

All-cause death in patients with multiple versus single arterial grafts according to SYNTAX score tertiles. Kaplan-Meier curves describing the probability of death up to 12.6 years follow-up in patients who underwent CABG and received multiple arterial grafts (MAG; red curve) versus single (SAG; blue curve) according to SYNTAX score tertiles; low (0-22; Panel A), intermediate (23-32; Panel B), and high (≥33; Panel C). The widths of 95% confidence intervals were not adjusted for multiple comparisons, therefore these intervals should not be used for inference about between-group differences. Abbreviations used: HR; hazard ratio, CI; confidence interval, MAG; multiple arterial grafts, SAG; single arterial graft.



Numbers at risk

MAG	465	453	444	437	422	408	388	375	368	358	350	296	146	46
SAG	1001	961	939	910	862	823	781	756	725	700	672	539	268	102

Graphical abstract.
All-cause death of patients with multiple arterial grafts versus a single arterial graft in the as-treated CABG cohort from the SYNTAX trial. Kaplan-Meier curves describing the probability of death up to 12.6 years follow-up in the overall cohort of patients who underwent CABG with multiple arterial grafts (red curve; n=465) versus a single arterial graft (blue curve; n=1001). *This result was confirmed with a weighted Cox proportional hazards model [HR : 0.75 95% CI (0.57 - 0.99) p = 0.04]. Abbreviations used: HR; hazard ratio, CI; confidence interval, MAG; multiple arterial grafts, SAG; single arterial graft.

DISCUSSION

CABG using multiple arterial grafts, compared to using a single arterial graft, was associated with lower all-cause death at 12.6 year follow-up in patients with *de novo* three-vessel and left main coronary artery disease from the SYNTAX trial. The significant survival benefit of using multiple arterial grafts remained after adjusting for differences in baseline characteristics (Graphical Abstract). This result was also confirmed with inverse probability weighed Cox regression. In pre-specified subgroups of patients with 3VD, LMCAD, those with diabetes and those without, CABG using multiple arterial grafts was associated with a significant survival benefit at 12.6-year follow-up. After adjusting for differences in baseline characteristics, MAG remained associated with a survival benefit for patients with 3VD, while no differences in all-cause death were found in patients with LMCAD and those with or without diabetes.

Although from a pathophysiological standpoint it is reasonable to expect that arterial grafts improve graft-patency and clinical outcomes compared with venous grafts, proof remains limited to observational data.[4, 7, 18-22] While the ART trial showed no difference in survival between bilateral versus single internal thoracic artery revascularisation multiple arterial grafting in the as-treated analyses demonstrated a significant survival benefit compared with a single arterial grafting strategy.(5) Some of the methodological limitations of the ART guided the design of the Randomized comparison of the clinical Outcome of single versus Multiple Arterial grafts (ROMA) trial which aims to determine the impact of using at least 2 arterial grafts to the left coronary system on 10-year survival in 4300 patients [23]; however, the first study results are unlikely to be published before 2025. Results reported in the present study are comparable to the as-treated MAG versus SAG 10-year all-cause death outcomes from the randomized ART trial (adjusted HR 0.81, 95% CI [0.68-0.95]).[6] Moreover, present data corresponds well with real-world data from large registries and single center studies that showed a significant reduction in all-cause death beyond 10year follow-up.[24, 25]

Pre-specified subgroup analysis revealed that MAG, compared with SAG, remained associated with significantly lower all-cause death in patients with 3VD, even after adjusting for differences in characteristics between groups. The adjusted, non-significant, HR in favor of MAG for patients with LMCAD (HR 0.85, 95%CI [0.54-1.34]) provides reassuring long-term insights that multiple arterial grafting is safe to perform in this specific patient population.[26]

The majority of patients with diabetes have diffuse and complex CAD. The present study found that 57% of patients with diabetes that received SAG have died during 12.6-year follow-up, versus 40% of patients who received MAG. This survival difference was associated with a significant, unadjusted, decreased risk of all-cause death in favor of MAG (HR 0.67, P=0.036). After adjusting for differences in baseline characteristics, this trend remained similar, yet was no longer significant. The propensity-matched analysis by Yamaguchi *et al.* reported decreased 12-year all-cause death rates with MAG versus SAG in patients with (35.1% vs 41.2%, P = 0.041) and without diabetes (28.6 vs 36.2%, P=0.014).[27] Furthermore, an increasing number of arterial grafts have been shown to have an incremental survival benefit in both patients with and without diabetes.[28]

Both the right internal thoracic artery and the radial artery have been associated with less adverse event and show a survival benefit compared with venous conduits.[1, 3, 21, 29] In the present study, 41% of patients in the MAG cohort received radial arteries and almost three-quarters received bilateral internal thoracic arteries (BITA). At 12.6 years, unadjusted all-cause death rates were significantly lower for patients that received BITA versus SITA and for those that received TAR versus no-TAR. A trend towards a survival benefit with BITA and TAR, compared with the use of a single artery, remained after adjusting for clinically and statistically relevant baseline differences. The use of additional arterial grafts in 245 patients (19.9%) in the no-TAR cohort may have skewed the survival outcomes in its favor following adjustment.

The major strength of the SYNTAX trial was that all patients were discussed in a multidisciplinary heart team, consisting of a cardiac surgeon, a clinical cardiologist and an interventional cardiologist. Prior to receiving either PCI or CABG, all significantly stenosed coronary vessels were assessed and those suitable for revascularisation determined. After myocardial revascularisation completeness of revascularisation was verified based on the number of vessels revascularized compared to those deemed suitable for revascularisation prior to intervention. The rate of complete revascularisation in both treatment groups in our study was lower than observed in previous studies.[30-32] These differences most certainly reflect the variation in definitions of completeness of revascularisation used across clinical trials, yet could also be partly explained by the greater anatomical complexity of coronary artery disease in patients included in the SYNTAX trial and in the nested CABG registry (higher burden of cardiovascular risk factors and a higher SYNTAX score). Severely calcified and diffusely diseased coronary arteries and small-sized (<2 mm) vessels distal to the lesion were the most common rationale for incomplete revascularisation in the CABG cohort of the SYNTAX trial. [33] Inability to graft such vessels is usually not associated with an increased risk of adverse events, which was clearly evident after 3-year follow-up of CABG patients in the SYNTAX trial who did not undergo complete revascularisation. Additional studies with longer follow-up (≥ 10-year) are warranted to determine the influence of complete revascularisation on clinical outcomes beyond 3 years.

Strengths and limitations

The high rate of completeness of follow-up and that follow-up is extended beyond 10 years are major strengths of the current study.

Results from this study should be considered as 'hypothesis-generating', as patients were not randomly allocated to undergo multiple versus single arterial grafting. Any influence of inter-institutional variation regarding patient selection, preferred surgical techniques and surgical experience could not be adequately corrected for.

Moreover, apart from well-designed randomized studies, none of the statistical methods that adjust for confounding factors are sufficient to fully account for confounders.[34] Furthermore, the modest sample size among subgroups of patients could have influenced results after adjusting for differences in baseline characteristics. Finally, the rate of incomplete revascularisation (approximately 28%) in combination with the suboptimal use of guideline directed medical treatment in patients from the SYNTAX trial could have diminished overall long-term survival in both cohorts.[10, 35]

CONCLUSION

In the present analysis of 1466 all-comers patients from the SYNTAX trial undergoing bypass surgery, CABG using a multiple arterial grafting strategy, as compared with using a single arterial graft, resulted in markedly lower incidence of all-cause death. This survival benefit of using MAG over SAG remained significant after adjusting for differences in important preselected patient characteristics between MAG and SAG. MAG in patients with three-vessel disease was associated with a significantly lower unadjusted and adjusted rate of all-cause death, while no statistically difference was identified in subgroups of patients with LMCAD and diabetes after adjusting for differences in important baseline variables. The markedly 12.6-year survival benefit of CABG using MAG over SAG in the SYNTAX trial strongly encourages a more extensive use of multiple arterial grafting in selected patients.

ACKNOWLEDGEMENTS

None.

FUNDING

The SYNTAX Extended Survival study was supported by the German Foundation of Heart Research (Frankfurt am Main, Germany). The SYNTAX trial, during 0-5 year follow-up, was funded by Boston Scientific Corporation (Marlborough, MA, USA). Both sponsors had no role in the study design, data collection, data analyses and interpretation of the study data, nor were involved in the decision to publish the final manuscript. The principal investigators and authors had complete scientific freedom.

CONFLICT OF INTEREST

Dr. Kappetein reports to work as employee of Medtronic, outside the submitted work. Dr. Serruys reports personal consultancy fees from Abbott Laboratories, Biosensors, Cardialysis, Medtronic, Micell, Sino Medical Sciences Technology, Philips/ Volcano, Xeltis and Heartflow. Dr. Mack reports non-financial support from Edwards Lifesciences, non-financial support from Medtronic and non-financial support from Abbott, outside the submitted work. Dr. Verberkmoes reports personal fees from Medtronic and personal fees from Atricure, outside the submitted work. Dr. Head reports to work as employee of Medtronic, outside the submitted work. All other authors report no potential conflict(s) of interest relevant to this publication.

Abbreviations

3VD #	three-vessel coronary artery disease
BITA #	bilateral internal thoracic artery
CABG #	coronary artery bypass grafting
CAD #	coronary artery disease
CI #	confidence interval
EuroSCORE #	The European System for Cardiac Operative Risk Evaluation
GHF #	German Heart Research Foundation
HR #	hazard ratio
IPTW #	inverse probability for treatment weights
LMCAD #	left main coronary artery disease
MAG #	multiple arterial grafting
SAG #	single arterial grafting
SITA #	single internal thoracic artery
SYNTAX #	Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery
SYNTAXES #	SYNTAX Extended Survival study
TAR #	total arterial revascularisation

REFERENCES

1. Taggart DP, D'Amico R and Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *The Lancet*. 2001;358:870-875.
2. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M and Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. *Ann Thorac Surg*. 2010;90:101-8.
3. Lytle BW, Blackstone EH, Sabik JF, Houghtaling P, Loop FD and Cosgrove DM. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. *Ann Thorac Surg*. 2004;78:2005-12; discussion 2012-4.
4. Buttar SN, Yan TD, Taggart DP and Tian DH. Long-term and short-term outcomes of using bilateral internal mammary artery grafting versus left internal mammary artery grafting: a meta-analysis. *Heart*. 2017;103:1419-1426.
5. Chikwe J, Sun E, Hannan EL, Itagaki S, Lee T, Adams DH and Egorova NN. Outcomes of Second Arterial Conduits in Patients Undergoing Multivessel Coronary Artery Bypass Graft Surgery. *J Am Coll Cardiol*. 2019;74:2238-2248.
6. Taggart DP, Benedetto U, Gerry S, Altman DG, Gray AM, Lees B, Gaudino M, Zamvar V, Bochenek A, Buxton B, Choong C, Clark S, Deja M, Desai J, Hasan R, Jasinski M, O'Keefe P, Moraes F, Pepper J, Seevanayagam S, Sudarshan C, Trivedi U, Wos S, Puskas J, Flather M and Arterial Revascularization Trial I. Bilateral versus Single Internal-Thoracic-Artery Grafts at 10 Years. *N Engl J Med*. 2019;380:437-446.
7. Goldman S, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, Thottapurathu L, Krasnicka B, Ellis N, Anderson RJ, Henderson W and Group VACS. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. *J Am Coll Cardiol*. 2004;44:2149-56.
8. Thuijs D, Kappetein AP, Serruys PW, Mohr FW, Morice MC, Mack MJ, Holmes DR, Jr., Curzen N, Davierwala P, Noack T, Milojevic M, Dawkins KD, da Costa BR, Juni P, Head SJ and Investigators SES. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet*. 2019.
9. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR, Jr., Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J and Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J*. 2006;151:1194-204.
10. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW and Investigators S. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-72.
11. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Stahle E, Dawkins KD, Mohr FW, Serruys PW and Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J*. 2011;32:2125-34.
12. Mohr FW, Morice M-C, Kappetein AP, Feldman TE, Ståhle E, Colombo A, Mack MJ, Holmes DR, Morel M-a, Dyck NV, Houle VM, Dawkins KD and Serruys PW. Coronary

artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *The Lancet*. 2013;381:629-638.

13. Parasca CA, Head SJ, Mohr FW, Mack MJ, Morice MC, Holmes DR, Jr., Feldman TE, Colombo A, Dawkins KD, Serruys PW, Kappetein AP and Investigators S. The impact of a second arterial graft on 5-year outcomes after coronary artery bypass grafting in the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery Trial and Registry. *J Thorac Cardiovasc Surg*. 2015;150:597-606 e2.
14. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW and Serruys PW. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1:219-27.
15. Sousa-Uva M, Neumann F-J, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO and Group ESCSD. 2018 ESC/EACTS Guidelines on myocardial revascularization. *European Journal of Cardio-Thoracic Surgery*. 2018:ezy289-ezy289.
16. Pocock SJ, Clayton TC and Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet*. 2002;359:1686-9.
17. Hickey GL, Dunning J, Seifert B, Sodeck G, Carr MJ, Burger HU, Beyersdorf F, Ejcts and Committees IE. Statistical and data reporting guidelines for the European Journal of Cardio-Thoracic Surgery and the Interactive CardioVascular and Thoracic Surgery. *Eur J Cardiothorac Surg*. 2015;48:180-93.
18. Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, McCarthy PM and Cosgrove DM. Two internal thoracic artery grafts are better than one. *J Thorac Cardiovasc Surg*. 1999;117:855-72.
19. Gaudino M, Rahouma M, Abouarab A, Tam DY, Di Franco A, Leonard J, Benedetto U, Iannaccone M, D'Ascenzo F, Biondi-Zoccai G, Vallely M, Girardi LN, Fremes SE and Taggart DP. Meta-Analysis Comparing Outcomes of Drug Eluting Stents Versus Single and Multiarterial Coronary Artery Bypass Grafting. *Am J Cardiol*. 2018;122:2018-2025.
20. Rocha RV, Tam DY, Karkhanis R, Nedadur R, Fang J, Tu JV, Gaudino M, Royse A and Fremes SE. Multiple Arterial Grafting Is Associated With Better Outcomes for Coronary Artery Bypass Grafting Patients. *Circulation*. 2018;138:2081-2090.
21. Schwann TA, Hashim SW, Badour S, Obeid M, Engoren M, Tranbaugh RF, Bonnell MR and Habib RH. 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 studydagger. *Eur J Cardiothorac Surg*. 2016;49:188-95.
22. Taggart DP, D'Amico R and Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet*. 2001;358:870-5.
23. Gaudino M, Alexander JH, Bakaeen FG, Ballman K, Barili F, Calafiore AM, Davierwala P, Goldman S, Kappetein P, Lorusso R, Mylotte D, Pagano D, Ruel M, Schwann T, Suma H, Taggart DP, Tranbaugh RF and Fremes S. Randomized comparison of the clinical outcome of single versus multiple arterial grafts: the ROMA trial-rationale and study protocol. *Eur J Cardiothorac Surg*. 2017.

24. Pu A, Ding L, Shin J, Price J, Skarsgard P, Wong DR, Bozinovski J, Fradet G and Abel JG. Long-term Outcomes of Multiple Arterial Coronary Artery Bypass Grafting: A Population-Based Study of Patients in British Columbia, Canada. *JAMA Cardiol*. 2017;2:1187-1196.
25. Locker C, Schaff HV, Dearani JA, Joyce LD, Park SJ, Burkhart HM, Suri RM, Greason KL, Stulak JM, Li Z and Daly RC. Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multi-vessel disease. *Circulation*. 2012;126:1023-30.
26. Thuijs D, Head SJ, Stone GW, Puskas JD, Taggart DP, Serruys PW, Dressler O, Crowley A, Brown WM, 3rd, Horkay F, Boonstra PW, Bogats G, Noiseux N, Sabik JF, 3rd and Kappetein AP. Outcomes following surgical revascularization with single versus bilateral internal thoracic arterial grafts in patients with left main coronary artery disease undergoing coronary artery bypass grafting: insights from the EXCEL trial. *Eur J Cardiothorac Surg*. 2018.
27. Yamaguchi A, Kimura N, Itoh S, Adachi K, Yuri K, Okamura H and Adachi H. Efficacy of multiple arterial coronary bypass grafting in patients with diabetes mellitus. *Eur J Cardiothorac Surg*. 2016;50:520-7.
28. Schwann TA, El Hage Sleiman AKM, Yammine MB, Tranbaugh RF, Engoren M, Bonnell MR and Habib RH. Incremental Value of Increasing Number of Arterial Grafts: The Effect of Diabetes Mellitus. *Ann Thorac Surg*. 2018;105:1737-1744.
29. Gaudino M, Benedetto U, Fremes S, Biondi-Zoccai G, Sedrakyan A, Puskas JD, Angelini GD, Buxton B, Frati G, Hare DL, Hayward P, Nasso G, Moat N, Peric M, Yoo KJ, Speziale G, Girardi LN, Taggart DP and Investigators R. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. *N Engl J Med*. 2018;378:2069-2077.
30. Briguori C, Condorelli G, Airoldi F, Focaccio A, D'Andrea D, Cannavale M, Abarghouei AA, Giordano S, De Vivo F, Ricciardelli B and Colombo A. Comparison of coronary drug-eluting stents versus coronary artery bypass grafting in patients with diabetes mellitus. *Am J Cardiol*. 2007;99:779-84.
31. Buszman PE, Kiesz SR, Bochenek A, Peszek-Przybyla E, Szkrobka I, Debinski M, Bialkowska B, Dudek D, Gruszka A, Zurakowski A, Milewski K, Wilczynski M, Rzeszutko L, Buszman P, Szymszal J, Martin JL and Tendera M. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol*. 2008;51:538-45.
32. Palmerini T, Barlocco F, Santarelli A, Bacchi-Reggiani L, Savini C, Baldini E, Alessi L, Ruffini M, Di Credico G, Piovaccari G, Di Bartolomeo R, Marzocchi A, Branzi A and De Servi S. A comparison between coronary artery bypass grafting surgery and drug eluting stent for the treatment of unprotected left main coronary artery disease in elderly patients (aged > or =75 years). *Eur Heart J*. 2007;28:2714-9.
33. Head SJ, Mack MJ, Holmes DR, Jr., Mohr FW, Morice MC, Serruys PW and Kappetein AP. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg*. 2012;41:535-41.
34. Milojevic M, Nikolic A, Jüni P and Head SJ. A statistical primer on subgroup analyses. *Interactive CardioVascular and Thoracic Surgery*. 2020.
35. Iqbal J, Zhang YJ, Holmes DR, Morice MC, Mack MJ, Kappetein AP, Feldman T, Stahle E, Escaned J, Banning AP, Gunn JP, Colombo A, Steyerberg EW, Mohr FW and Serruys PW. Optimal medical therapy improves clinical outcomes in patients undergoing revascu-

larization with percutaneous coronary intervention or coronary artery bypass grafting: insights from the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial at the 5-year follow-up. *Circulation*. 2015;131:1269-77.

SUPPLEMENTARY MATERIALS

Statistical analysis – Propensity score method:

A propensity sore adjusted weighting was performed as a sensitivity analysis to further confirm results obtained with the multi-variable Cox model. This study included 1466 patients at 84 different centers. The median number of procedures performed by each center was 16 (interquartile range 9 – 24). MAG was performed by 62 different hospitals. From all patients operated at a specific center, a median of 6 (interquartile range 2 - 10) patients in that center underwent multi-arterial grafting. In order to adjust for this large variation in grafting strategies, center volume was included in the model developed to calculate the propensity score. Centers were, therefore, grouped according to MAG into (1) low volume: 1 - 10 procedures contributed (2) moderate volume: 11 - 20 procedures contributed (3) high volume: > 20 procedures contributed (Supplement Figure 1). A generalized linear mixed model (hierarchical model) was developed with two levels; level 1 - clinical covariates as fixed effects and level 2 - grouping indicator for MAG procedure volume fit as a random intercept. The clinical covariates included in the model were: age at surgery, sex, obesity (BMI > 30), hypertension, hyperlipidemia, prior myocardial infarction, prior stroke, medically treated diabetes, PAD, COPD, smoking, chronic kidney disease, low LVEF, CAD, unstable angina, left main disease, syntax score and logistic Euroscore. Given the importance of both age and the SYNTAX score on long term survival, both these continuous variables were fit as natural splines (with 3 degrees of freedom). The logistic Euroscore was fit as a linear term in the model. The variables with observed missing proportion are as follows: obesity 0.06%, hypertension 1.15%, hyperlipidemia 1.5%, prior myocardial infarction 1.7%, prior stroke 0.4%, smoking 0.6%, SYNTAX score 1.1% and low LVEF 0.3%. As seen, missing data was very limited. Hence, the mean and mode were used to fill missing values for continuous and categorical variables respectively.

After confirming model diagnostics, fitted values derived from the model provide the marginal likelihood for each patient to receive MAG rather than SAG. A significant difference in sample sizes between groups (MAG - 465 & SAG - 1001) was observed, hence, propensity score derived weighting methods were chosen as the preferred method[1].

To obtain the adjusted association of MAG with long-term survival, the average treatment effect (ATE)/IPTW (Inverse Probability of Treatment Weight) weights were calculated for each patient. Briefly, the IPTW weights were calculated as:

1. for the treated (MAG) = 1/ps
2. For the control (SAG) = 1/(1 - ps) where ps = propensity score.

When using IPTW, patients with very low ps scores in the treated group, or very high ps scores in the control group have unusually high weights. These weights can be considered as outliers; thus, it is recommended to use either stabilized weights or truncated weights rather than the calculated IPTW raw weights [2]. We chose to use truncated weights; hence, the range of IPTW weights were limited to their 1st and 99th percentile. Any value beyond these limits were set to the 1st or 99th percentile as appropriate. To determine balance before and after weighting, standardized differences for each co-variate were compared. With the derived truncated weights, a weighted Cox proportional hazards model was fit to evaluate the marginal long-term survival benefit of MAG compared to SAG. The model fulfills the proportional hazards assumption. Results are presented as hazard ratio at the 95% confidence level.

Supplement Figures:

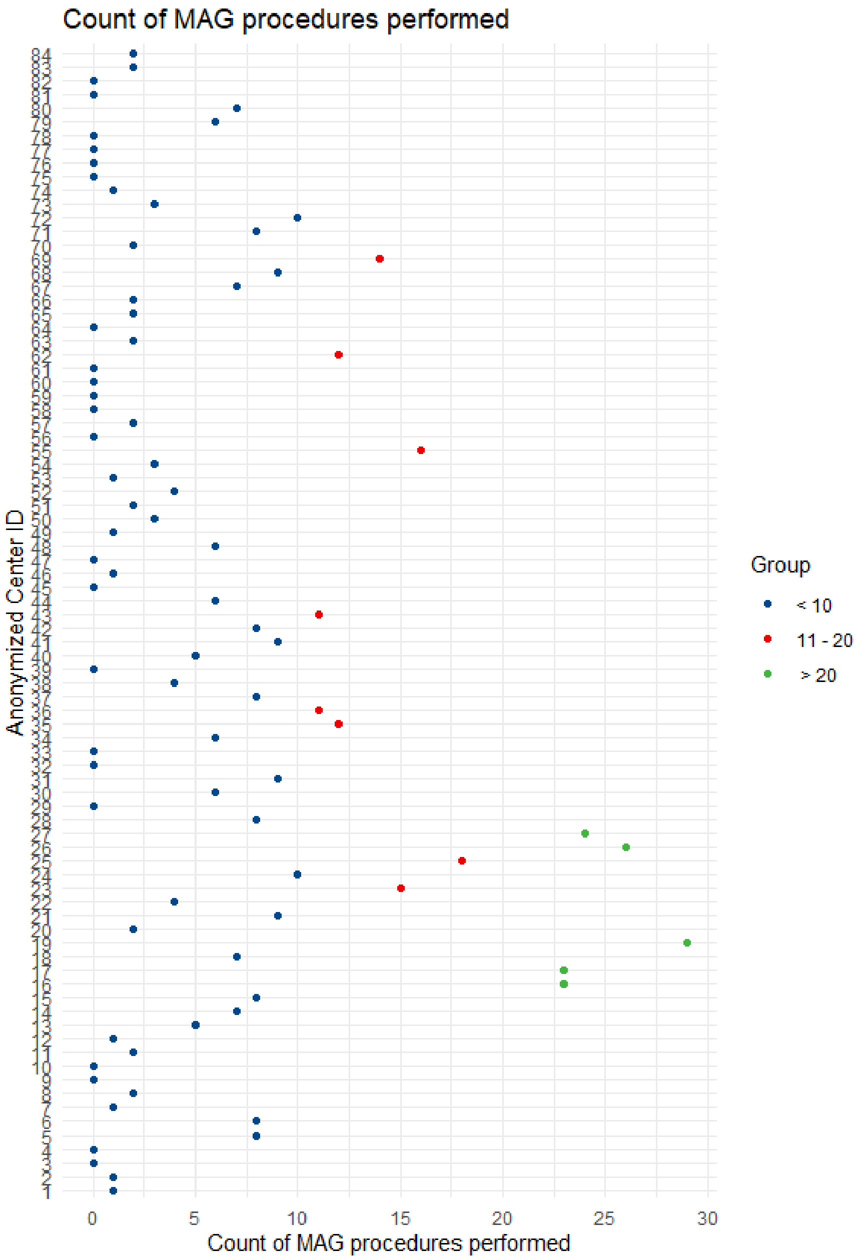


Figure S1. Total number of MAG performed at each center enrolled in the SYNTAX study. This dot chart presents the total number of MAG procedures performed at each of the 85 centers that contribute data to our study. As depicted, five centers performed more than 20 procedures each (green dots), while 8 hospitals contributed between 11 – 20 patients each (red dots).
Abbreviations used: MAG; multiple arterial grafting.

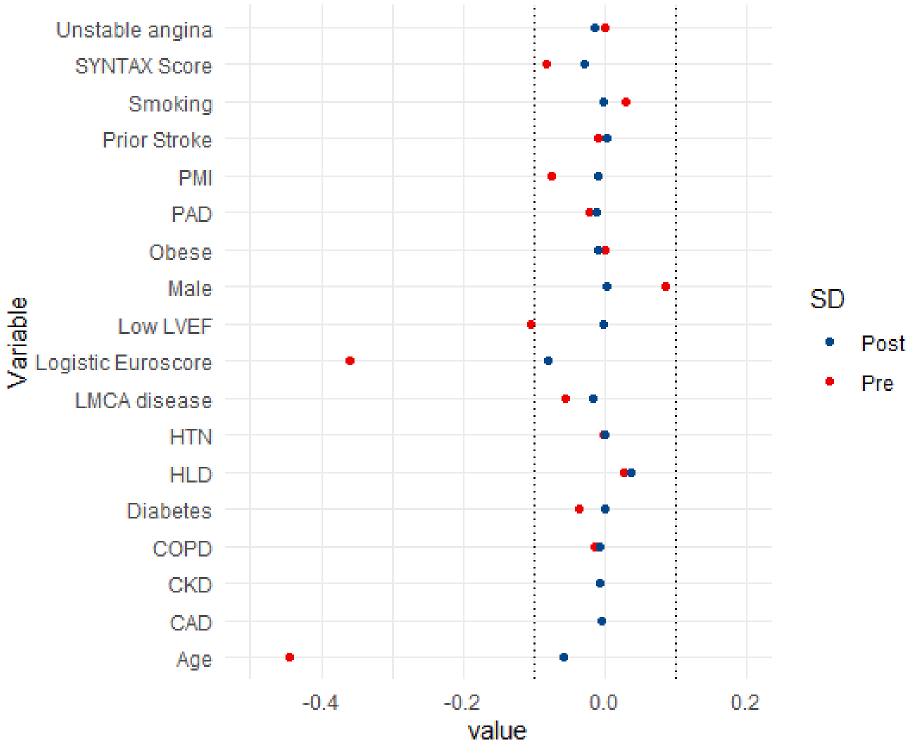


Figure S2. The standardized differences for all the variables included as fixed covariates in the mixed effects model to derive the propensity score. The standardized difference for all co-variates included in our mixed model were calculated to compute the propensity score. The red dots and blue dots depict SD pre- and post-weighting respectively. As depicted, after weighting, all variables have an absolute post-weighting SD < 0.1. Hence, one can assume that these weights are able to neutralize the imbalance in clinical co-variates between the MAG and SAG groups.
Abbreviations used: PMI ; periprocedural myocardial infarction, PAD; peripheral arterial disease, LVEF: left ventricular ejection fraction, LMCA; left main coronary artery disease, HTN; hypertension, HLD; hyperlipidemia, COPD; chronic obstructive pulmonary disease, CKD: chronic kidney disease, CAD: coronary artery disease.

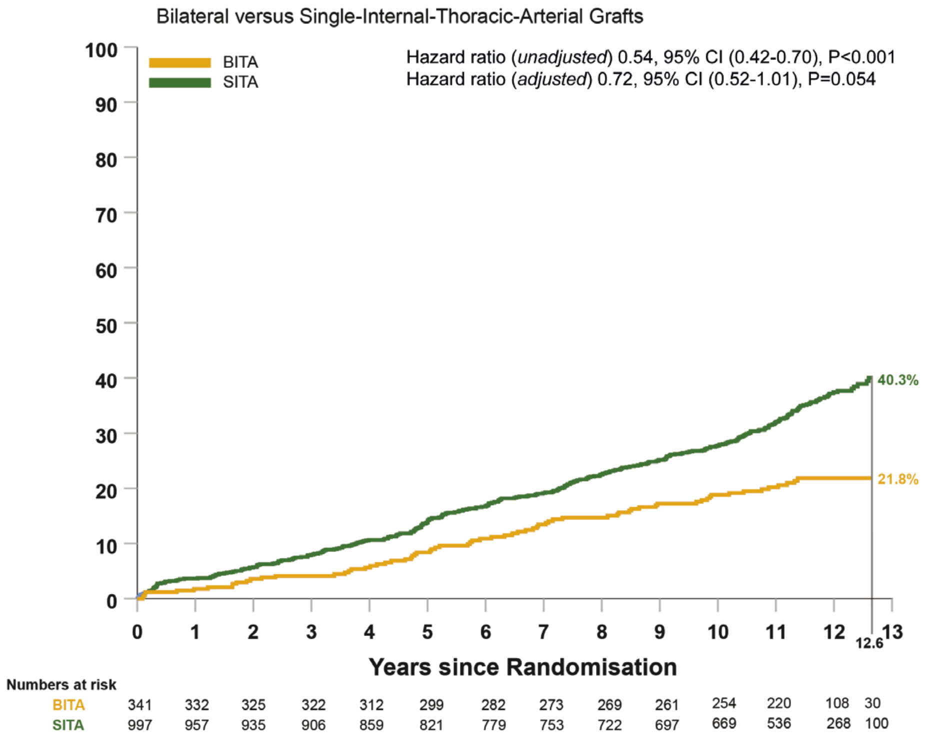
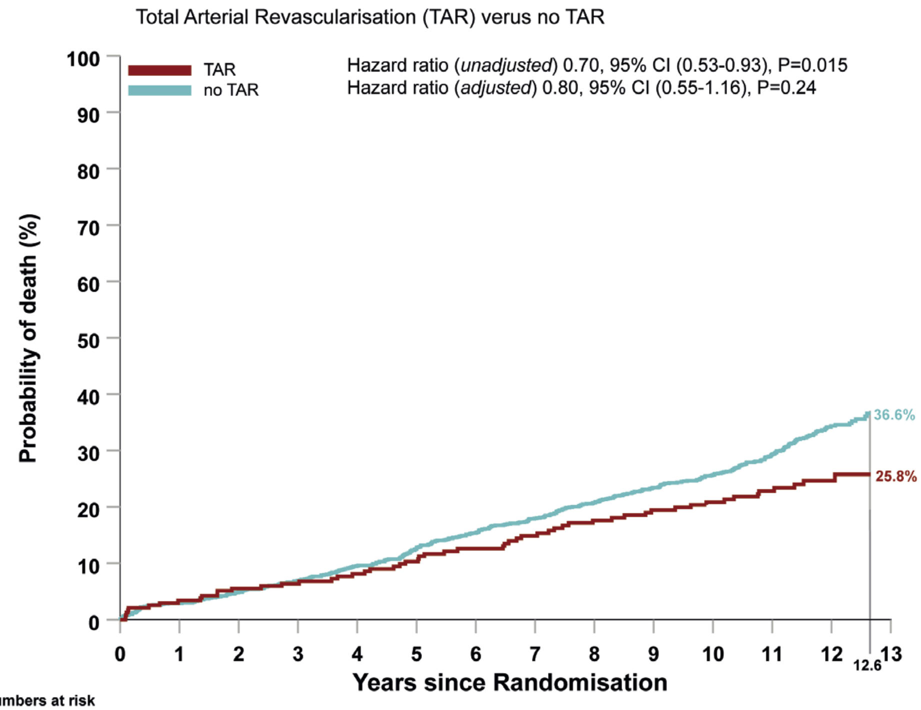


Figure S3. All-cause death in patients who received Bilateral versus Single-Internal-Thoracic-Artery revascularisation Kaplan-Meier curves describing the probability of death up to 12.6 years follow-up in patients who underwent CABG and received BITA (orange curve) versus SITA (green curve). Variables used in the full multivariable Cox regression analysis: age, sex, hypertension, hyperlipidemia, stroke or TIA, diabetes mellitus, peripheral vascular disease, carotid artery disease, chronic obstructive pulmonary disease, creatinine >200micromol/L, left ventricular ejection fraction<50% and SYNTAX score (as a continuous variable). The widths of 95% confidence intervals were not adjusted for multiple comparisons, therefore these intervals should not be used for inference about between-group differences.

Abbreviations used: BITA: bilateral-internal-thoracic-arteries, SITA: single-internal-thoracic-artery, HR; hazard ratio, CI; confidence interval.



Numbers at risk

TAR	234	226	221	219	210	202	192	186	180	176	170	131	73	26
no TAR	1232	1188	1162	1128	1074	1030	978	945	913	882	852	693	341	121

Figure S4. All-cause death in patients who received Total Arterial Revascularisation (TAR) versus no TAR. Kaplan-Meier curves describing the probability of death up to 12.6 years follow-up in patients who underwent CABG and received TAR (burgundy curve) versus no TAR (turquoise curve). Variables used in the full multivariable Cox regression analysis: age, sex, hypertension, hyperlipidemia, stroke or TIA, diabetes mellitus, peripheral vascular disease, carotid artery disease, chronic obstructive pulmonary disease, creatinine >200micromol/L, left ventricular ejection fraction<50% and SYNTAX score (as a continuous variable). The widths of 95% confidence intervals were not adjusted for multiple comparisons, therefore these intervals should not be used for inference about between-group differences.

Abbreviations used: BITA: bilateral-internal-thoracic-arteries, SITA: single-internal-thoracic-artery, HR; hazard ratio, CI; confidence interval.

SUPPLEMENT REFERENCES:

1. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424. doi: 10.1080/00273171.2011.568786
2. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-3679. doi:10.1002/sim.6607

PACKAGES USED FOR ANALYSIS:

1. survival-package, A Package for Survival Analysis in R. Terry M Therneau 2020
R package version 3.2-3 https://CRAN.R-project.org/package=survival},
2. cobalt : Noah Greifer (2020). cobalt: Covariate Balance Tables and Plots.
R package version 4.2.2. https://CRAN.R-project.org/package=cobalt
3.tidvyerse - Wickham et al., (2019). Welcome to the tidyverse. Journal of Open Source Software, 4(43), 1686, https://doi.org/10.21105/joss.01686
4. splines - R Core Team (2008) R: A language and environment for statistical computing. R foundation for Statistical Computing. Vienna, Austria.
5.lme4 - Douglas Bates, Martin Maechler, Ben Bolker, Steve Walker (2015).
Fitting Linear Mixed-Effects Models using lme4. Journal of Statistical Software, 67(1). 1 - 48. doi: 10.18637/jss.v067.i01