

Association of age with 10-year outcomes after coronary surgery in the Arterial Revascularization Trial

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Abstract

Background: The association of age with the outcomes of bilateral vs single internal thoracic arteries (BITA vs SITA) for coronary bypass surgery (CABG) remains to be determined.

Objectives: We evaluated the association between age and the BITA vs SITA outcomes in the Arterial Revascularization Trial.

Methods: The primary endpoints were all-cause mortality and a composite of major adverse events (MAE) including all-cause mortality, myocardial infarction or stroke. Secondary endpoints were bleeding complications and sternal wound complications up to 6 months after surgery. Multivariable fractional polynomials analysis and log-rank tests were used.

Results: Age did not affect any of the explored outcomes in the overall BITA vs SITA comparison in the intention-to-treat analysis and in the analysis based on the number of arterial grafts received. However, when the intention-to-treat analysis was restricted to the populations of patients between 50 and 70 years, younger patients in the BITA arm had a significantly lower incidence of MAE ($p=0.03$).

Conclusions: Our results suggest that BITA may improve long-term outcome in younger patients, although more randomized data are needed to confirm this hypothesis.

Key words: CABG, bilateral internal thoracic arteries, single internal thoracic artery

Condensed abstract

In the Arterial Revascularization Trial, younger patients in the bilateral internal thoracic artery arm had better long-term outcomes, but this need to be confirmed in larger trials.

Abbreviations:

BITA, bilateral internal thoracic artery

SITA, single internal thoracic artery

CABG, coronary artery bypass grafting

ART, Arterial Revascularisation Trial

RCT, randomised controlled trial

MFP, multivariable fractional polynomials

HR, hazard ratio

ROMA, Randomized comparison of the Outcome of single vs Multiple Arterial grafting trial

Introduction

Observational studies and meta-analyses have suggested that patients who receive bilateral instead of single internal thoracic arteries (BITA vs SITA) for coronary artery bypass grafting (CABG) have better long term outcomes, including mortality.(1,2)

The Arterial Revascularisation Trial (ART) is the only large randomised controlled trial (RCT) to compare outcomes of BITA vs SITA grafting in patients undergoing CABG.(3) The trial randomized 3102 patients to one of the two treatment arms and at 10-year follow-up survival data were available for 97.7% of the patients. In the intention-to-treat analysis, no significant difference was found in all-cause mortality or in the composite outcome of all-cause mortality, stroke or myocardial infarction. Because of the high crossover and co-intervention rates (use of the radial artery in the control group in particular), a post-hoc analysis based on the number of arterial grafts received was also performed and showed higher survival and event-free survival in the multiple arterial grafts group.

Observational evidence suggests that the long-term benefit of multiple arterial grafting may become apparent only at long-term follow-up and it has been suggested that the beneficial effects of the BITA grafting strategy may be seen only in younger patients.(4–6) The interaction of treatment with age was not fully investigated in the ART trial, as only the subgroup of patients 70 years or older in the intention-to treat analysis was explored. The current analysis is designed to provide a more detailed assessment of the association of age with the outcomes of BITA vs SITA grafting in ART using pre-defined trial outcomes.

In addition, from a methodological perspective, ART provides a unique opportunity to assess the rate of cardiac events by age in a large cohort of CABG patients followed for 10 years. The resulting estimates may be important to assess whether the treatment effect in older patients is obscured by the competing risks of non-cardiac mortality which may inform the design of future CABG trials. The secondary aim of this analysis is to provide estimates of

event rates by age group based on the CABG trial with the longest and most complete follow-up to date.

Methods

The ART trial

The ART trial (3) was a two-group, multicentre, unblinded, RCT conducted in 28 hospitals across 7 countries. The trial complied with the principles of the Declaration of Helsinki and commenced after ethics approval was obtained at all the participating centers.

Eligible patients were randomised equally between two surgical strategies – BITA or SITA grafting. The primary outcome was all-cause mortality. Secondary outcomes included a composite of all-cause mortality, myocardial infarction or stroke, cardiac mortality, repeat revascularization, and safety outcomes (including bleeding events and sternal wound complications). In ART events were adjudicated by an independent clinical event review committee. Details of the outcome definitions and of the adjudication process used in ART are provided in the **Appendix**.

Present analysis

The present analysis is based on data collected from the ART trial up to 10 years post randomization and analysed as intention-to-treat. Age was analysed both as a categorical variable by decade and as a continuous variable.

For the first aim of the analysis (to provide a more detailed assessment of the association of age with the outcomes of BITA vs SITA grafting in ART using pre-defined trial outcomes), we used the Royston and Sauerbrei approach(7) with multivariable fractional polynomials (MFP) to model the treatment by age interaction on the primary and secondary outcomes.

This method avoids the disadvantages associated with dichotomising the data, such as decreased power and a possible increase in the false positive rate resulting from the creation of “optimal” cut points. An MFP was estimated to represent the hazard ratio (HR) of an outcome with respect to age, while adjusting for other covariates. The difference between the

MFP functions for the two treatment groups was tested using the interaction between treatment and the MFP function. This analysis is illustrated in a ‘treatment-effect plot’ of the difference (Log HR) against age and the 95% confidence interval (CI). Consistent with the main trial, the primary endpoints for this analysis were all-cause mortality and a composite of major adverse events (MAE) including all-cause mortality, myocardial infarction or stroke. Secondary endpoints were bleeding complications and sternal wound complications up to 6 months post-procedure.

In addition, we performed a sub-analysis for the MAE outcome limited to patients between 50 and 70 years of age. The rationale for the focus on this specific subgroup and outcome was both clinical (as this is the age group that is most commonly represented among CABG patients and the one where equipoise between the use of SITA vs BITA is stronger) and statistical (as the use of this age range and outcome maximizes the power of this sub-analysis).

For the second aim (to provide estimates of event rates by age group), a descriptive analysis was conducted. The treatment groups were pooled, as there was no treatment effect in the main trial analysis, and age was analysed as a categorical variable (by decade). Kaplan-Meier curves and the log-rank test were used to describe outcomes. For cardiac mortality and non-fatal events the cumulative incidence with non-cardiac mortality and mortality as competing risks respectively were estimated and compared using the Gray test.⁽⁸⁾ Endpoints for this analysis were all-cause mortality, cardiac mortality and a composite of non-fatal cardiac events including myocardial infarction and repeat revascularization.

Because of the high crossover and co-intervention rate,⁽⁹⁾ in the original publication the results of ART were also presented comparing outcomes in patients who received single vs

multiple arterial grafts.(3) As a sensitivity analysis, we repeated the analysis for the first aim using the same approach.

All analyses were performed using Stata V14 and SAS V9.4 (SAS Institute, Inc).

Results

General sample characteristics

Baseline characteristics of patients in the ART trial, operative details, and sample sizes by age category are reported in **Table 1**.(10) The median (Q1-Q3) follow-up time was 10.00 years (9.98-10.00).

Effect of age on the outcomes of BITA vs SITA grafting

For all-cause mortality (**Figure 1**), the logarithm of the HR of BITA relative to SITA remained close to zero across all ages, indicating no significant interaction ($p = 0.98$). For the composite outcome (**Figure 2**), a trend was noted suggesting improved outcomes for younger patients undergoing BITA compared to SITA (logarithm of HR negative for younger patients and positive for older patients) consistent with the Kaplan-Meier curves for the composite outcome in the categorical analysis (**Supplementary Figure 1**). However, in the overall analysis the confidence band overlapped zero throughout and the interaction was not significant ($p = 0.18$).

In the analysis restricted to the population of patients between 50 and 70 years, younger patients in the BITA arm had a significantly lower incidence of MAE ($p = 0.03$, **Figure 3**). For sternal wound infection rates at 6 months (**Supplementary Figure 2**), the logarithm of odds ratios (ORs) remained close to approximately 0.75 across all ages and there was no significant interaction with age ($p = 0.61$). Similarly, for bleeding rates (**Supplementary Figure 3**) the confidence band overlapped zero throughout all ages and the interaction with age was not significant ($p = 0.78$).

The results of the analysis based on the number of arterial grafts were consistent with the main analysis (**Supplementary Figures 4-7**).

Descriptive analysis by age group

Results for the descriptive analysis for the whole cohort divided into decades of age is summarised for all-cause mortality (**Figure 4A**), cardiac mortality (**Figure 4B**), and myocardial infarction and repeat revascularization (**Figure 4C**), respectively.

The analysis shows that the 10-year rates of all-cause mortality after CABG increase with age. A similar trend was observed for cardiac mortality despite the competing risk of mortality from other causes, indicating that mortality due to cardiovascular events increases with older age and is especially high in the >80 years subgroup. In contrast, no difference across age for the composite of non-fatal cardiac events, especially across the 51–75 years subgroups was found.

Discussion

In this exploratory analysis of the 10-year data from the ART trial we found no overall effect of age on the relative effect of BITA and SITA for all-cause mortality, MAE, sternal wound infections or risk of bleeding. However, when the analysis was restricted to the populations of patients between 50 and 70 years, younger patients in the BITA arm had a significantly lower incidence of MAE.

Observational studies have suggested that the benefit of BITA grafting may be age-dependent. The increase in non-cardiac mortality with increasing age and a shorter life expectancy in older patients may minimize any cardiac survival benefit gained with BITA compared to SITA. Kieser and colleagues using spline analysis found that after a mean follow up of 7 years, BITA grafting was associated with improved outcomes in patients up to age 70, but not after age 70.(4) Similar findings were reported by Benedetto et al. who found that survival benefit of BITA was improved through age 69 years, but not afterwards.(5) In a propensity matched analysis of over 9,000 patients the protective effect of radial artery grafting on late survival progressively decreased with patient age starting at around age 60 years, and was no longer observed at the age of 70 years.(6) In a recent analysis of more than 26,000 patients in a state-mandated database in New Jersey, the use of multiple arterial grafts was associated with better 10-year clinical outcomes, including survival, but this benefit was not evident for patients 70 years and older.(11)

Our results are based on the CABG trial with the longest and most complete follow-up to date and support the hypothesis of an age-specific effect of BITA, with younger patients deriving the largest benefit from its use. Compared to the previous observational studies, our results are based on data of higher quality and granularity that allow for better adjustment for confounders.(12) However, our findings need confirmation in larger trials focused on young patients. The Randomized comparison of the Outcome of single vs Multiple Arterial grafting

(ROMA) trial has an age cut-off of 70-years for patients inclusion and will provide additional important insights on the effect of multiple arterial grafts in a relatively young patient cohort.

(13)

In addition, the described lack of effect of age on the risk of sternal and bleeding complications after BITA is an important and reassuring finding for surgeons that use BITA in older patients.

The ART database also provided an unique opportunity to evaluate the association of age with 10-year mortality and other outcomes in CABG patients. Our data show that while all-cause mortality and cardiac mortality increase with age, no interaction with age exists for non-cardiac events.

While the increase in all-cause mortality with age is expected, the increase in cardiac mortality has at least two possible explanations. It is possible that non-cardiac deaths were erroneously coded as cardiac - the risk of erroneous adjudication of cause-specific mortality has been well described before,(14,15) and the adjudication of cardiovascular deaths in particular has been shown to vary substantially across assessors.(16) Alternatively, it is possible that cardiac events are more likely to be fatal in older patients due to reduced myocardial and other key organ functional reserve with aging. These data are important to inform the design and sample size calculations of future CABG trials.

There are limitations to our analysis. First, this is a post hoc analysis carried out after the main results have been available which can introduce bias. Second, although ART enrolled more than 3000 patients followed for ten years, there is limited power to explore effects of BITA and SITA grafting in subgroups. Finally, the possible role of the high crossover and co-intervention rates in ART have been extensively discussed, as well as the limitations of the analysis based on the number of arterial grafts.(9)

In conclusion, our results suggest that younger patients may especially benefit from BITA grafting, but more randomized data are needed to confirm this hypothesis.

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Figure Legends

Figure 1. Treatment-effect plot for interaction between BITA vs SITA and age on 10 year all-cause mortality (the shading corresponds to the 95% confidence interval for the log HR at the corresponding age). BITA, bilateral internal thoracic arteries; HR, hazard ratio; SITA, single internal thoracic artery.

Figure 2. Treatment-effect plot for interaction between the 10-year composite outcome (all-cause mortality, myocardial infarction or stroke) of BITA vs SITA with age (the shading corresponds to the 95% confidence interval for the log HR at the corresponding age). BITA, bilateral internal thoracic arteries; HR, hazard ratio; SITA, single internal thoracic artery.

Figure 3 (Central Illustration). Treatment-effect plot for interaction between the 10-year composite outcome (all-cause mortality, myocardial infarction or stroke) of BITA vs SITA with age in patients between 50 and 70 years (the shading corresponds to the 95% confidence interval for the log HR at the corresponding age). BITA, bilateral internal thoracic arteries; HR, hazard ratio; SITA, single internal thoracic artery.

Figure 4. Results for the descriptive analysis for the whole cohort divided by decades of age. Panel A: All-cause mortality by age group; Panel B: Cumulative Incidence of cardiac mortality by age group; Panel C: Cumulative incidence of myocardial infarction and repeat revascularization by age group.

Clinical Perspectives

Medical knowledge: In the Arterial Revascularization Trial, younger patients in the bilateral internal thoracic artery arm had better long-term outcome, although this needs to be confirmed in larger trials.

Translational outlook: These data have important implications for conduit selection in coronary bypass surgery. Future trials testing the arterial graft hypothesis must focus on the younger patients who are more likely to benefit from the intervention.

Table 1. Patient characteristics in the Arterial Revascularization Trial.
Adapted from Taggart et. al. N Engl J Med 2016; 375:2540-2549

	Overall (N = 3102)	Single ITA Group (N = 1554)	Bilateral ITA Group (N = 1548)
Age at randomization (mean±standard deviation – yr)	63.1±8.9	63.0±9.1	63.2±8.7
Age categories in years – no. (%)			
30-40	21 (0.7)	11 (0.7)	10 (0.6)
41-50	266 (8.6)	135 (8.7)	131 (8.5)
51-60	910 (29.3)	475 (30.6)	435 (28.1)
61-70	1200 (38.7)	577 (37.1)	623 (40.2)
71-75	468 (15.1)	238 (15.3)	230 (14.9)
76-80	209 (6.7)	97 (6.2)	112 (7.2)
81+	28 (0.9)	14 (0.9)	14 (0.9)
Male sex — no. (%)	2656 (85.6)	1338 (86.1)	1318 (85.1)
Smoking status — no. (%)			
Current smoking	451 (14.5)	214 (13.8)	237 (15.3)
Former smoking	1732 (55.8)	898 (57.8)	834 (53.9)
Never smoked	919 (29.6)	442 (28.4)	477 (30.8)
Diabetes — no. (%)			
No history	2368 (76.3)	1191 (76.6)	1177 (76.0)
Insulin-dependent diabetes	174 (5.6)	79 (5.1)	95 (6.1)
Non-insulin-dependent diabetes	560 (18)	284 (18.3)	276 (17.8)
Hypertension (drug-treated) — no. (%)	2410 (77.7)	1217 (78.3)	1193 (77.1)
Hyperlipidemia (drug-treated) — no./total no. (%)	2905/3101 (93.6)	1448/1554 (93.2)	1457/1547 (94.2)
Peripheral arterial disease — no. (%)	221 (7.1)	118 (7.6)	103 (6.7)
Previous stroke — no./total no. (%)	90/3101 (2.9)	48/1553 (3.1)	42/1548 (2.7)
Previous myocardial infarction — no./total no. (%)	1300/3100 (41.9)	681/1553 (43.9)	619/1547 (40.0)
Use of cardiopulmonary bypass			
Yes	1818/3077 (59.1)	928/1546 (60.0)	890/1531 (58.1)
No	1259/3077 (40.9)	618/1546 (40.0)	641/1531 (41.9)
Number of vessels grafted — no./total no. (%)			

1	19/3076 (0.6)	11/1546 (0.7)	8/1530 (0.5)
2	545/3076 (17.7)	273/1546 (17.7)	272/1530 (17.8)
3	1520/3076 (49.4)	749/1546 (48.5)	771/1530 (50.4)
4+	992/3076 (32.2)	513/1546 (33.2)	479/1530 (31.3)
Radial artery graft — no./total no. (%)	639/3076 (20.8)	339/1546 (21.8)	300/1530 (19.4)
Target vessel for the radial artery			
Left anterior descending artery system — no./total no. (%)	166/800 (20.8)	107/467 (22.9)	59/333 (17.7)
Circumflex coronary artery — no./total no. (%)	336/800 (42.0)	259/467 (55.5)	77/333 (23.1)
Right coronary artery — no./total no. (%)	298/800 (37.3)	101/467 (21.6)	197/333 (59.2)
Target vessel for the right internal thoracic artery			
Left anterior descending artery system — no./total no. (%)	813/1428 (56.9)	42/62 (67.7)	771/1366 (56.4)
Circumflex coronary artery system — no./total no. (%)	564/1428 (39.5)	16/62 (25.8)	548/1366 (40.1)
Right coronary artery system — no./total no. (%)	51/1428 (3.6)	4/62 (6.5)	47/1366 (3.4)

ITA, internal thoracic artery.