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# Association of Age With 10-Year Outcomes After Coronary Surgery in the Arterial Revascularization Trial

Mario Gaudino, MD, MSCE,[a] Antonino Di Franco, MD,[a] Marcus Flather, MBBS,[b] Stephen Gerry, MSc,[c] Emilia Bagiella, PhD,[d] Alastair Gray, PhD,[e] Leon Pearcey, MBBS,[b] Teng-Hui Saw, MSc,[b] Belinda Lees, BSc, PhD,[f] Umberto Benedetto, MD,[g] Stephen E. Fremes, MD,[h] David P. Taggart, MD, PhD[f]

## ABSTRACT

**BACKGROUND** The association of age with the outcomes of bilateral internal thoracic arteries (BITAs) versus single internal thoracic arteries (SITAs) for coronary bypass grafting (CABG) remains to be determined.

**OBJECTIVES** The purpose of this study was to evaluate the association between age and BITA versus SITA outcomes in the Arterial Revascularization Trial.

**METHODS** The primary endpoints were all-cause mortality and a composite of major adverse events, 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 versus 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 age 50 and 70 years, younger patients in the BITA arm had a significantly lower incidence of major adverse events ($p = 0.03$).

**CONCLUSIONS** Our results suggest that BITA may improve long-term outcome in younger patients, although more randomized data are needed to confirm this hypothesis. (J Am Coll Cardiol 2021;77:18–26) © 2021 by the American College of Cardiology Foundation.

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

The ART (Arterial Revascularisation Trial) is the only large randomized controlled trial (RCT) to compare outcomes of BITA versus SITA grafting in patients undergoing CABG (3). The trial randomized 3,102 patients to 1 of the 2 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 cointervention rates (use



From the [a]Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York City, New York, USA; [b]Norwich Medical School, University of East Anglia, Norwich, United Kingdom; [c]Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom; [d]Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, New York, USA; [e]Department of Public Health, Health Economics Research Centre, University of Oxford, Oxford, United Kingdom; [f]Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom; [g]Bristol Heart Institute, University of Bristol, School of Clinical Sciences, United Kingdom; and the [h]Department of Surgery, Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada. Joanna Chikwe, MD, served as Guest Associate Editor for this paper. Athena Poppas, MD, served as Guest Editor-in-Chief for this paper.

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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 versus 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 noncardiac 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 2-group, multicenter, 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 participating centers.

Eligible patients were randomized equally between 2 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 Supplemental Appendix.

**PRESENT ANALYSIS.** The present analysis is based on data collected from the ART trial up to 10 years post randomization and analyzed as intention-to-treat. Age was analyzed 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 versus 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 dichotomizing 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 2 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.

**ABBREVIATIONS AND ACRONYMS**

**BITA** = bilateral internal thoracic artery

**CABG** = coronary artery bypass grafting

**HR** = hazard ratio

**MFP** = multivariable fractional polynomials

**RCT** = randomized controlled trial

**SITA** = single internal thoracic artery

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In addition, we performed a subanalysis 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 subanalysis).

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 analyzed as a categorical variable (by decade). Kaplan-Meier curves and the log-rank test were used to describe outcomes. For cardiac mortality and nonfatal events, the cumulative incidence with noncardiac 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 nonfatal cardiac events including myocardial infarction and repeat revascularization.

Because of the high crossover and cointervention rate (9), in the original publication, the results of ART were also presented comparing outcomes in patients who received single versus multiple arterial grafts (3).

**TABLE 1 Patient Characteristics in the Arterial Revascularization Trial**

| | Overall (N = 3,102) | Single ITA Group (n = 1,554) | Bilateral ITA Group (n = 1,548) |
|---|---|---|---|
| Age at randomization, yrs | 63.1 ± 8.9 | 63.0 ± 9.1 | 63.2 ± 8.7 |
| Age categories in yrs | | | |
| 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 | 1,200 (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 | 2,656 (85.6) | 1,338 (86.1) | 1,318 (85.1) |
| Smoking status | | | |
| Current smoking | 451 (14.5) | 214 (13.8) | 237 (15.3) |
| Former smoking | 1,732 (55.8) | 898 (57.8) | 834 (53.9) |
| Never smoked | 919 (29.6) | 442 (28.4) | 477 (30.8) |
| Diabetes | | | |
| No history | 2,368 (76.3) | 1,191 (76.6) | 1,177 (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) | 2,410 (77.7) | 1,217 (78.3) | 1,193 (77.1) |
| Hyperlipidemia (drug-treated) | 2,905/3,101 (93.6) | 1,448/1,554 (93.2) | 1,457/1,547 (94.2) |
| Peripheral arterial disease | 221 (7.1) | 118 (7.6) | 103 (6.7) |
| Previous stroke | 90/3,101 (2.9) | 48/1,553 (3.1) | 42/1,548 (2.7) |
| Previous myocardial infarction | 1,300/3,100 (41.9) | 681/1,553 (43.9) | 619/1,547 (40.0) |
| Use of cardiopulmonary bypass | | | |
| Yes | 1,818/3,077 (59.1) | 928/1,546 (60.0) | 890/1,531 (58.1) |
| No | 1,259/3,077 (40.9) | 618/1,546 (40.0) | 641/1,531 (41.9) |
| Number of vessels grafted | | | |
| 1 | 19/3,076 (0.6) | 11/1,546 (0.7) | 8/1,530 (0.5) |
| 2 | 545/3,076 (17.7) | 273/1,546 (17.7) | 272/1,530 (17.8) |
| 3 | 1,520/3,076 (49.4) | 749/1,546 (48.5) | 771/1,530 (50.4) |
| 4+ | 992/3,076 (32.2) | 513/1,546 (33.2) | 479/1,530 (31.3) |
| Radial artery graft | 639/3,076 (20.8) | 339/1,546 (21.8) | 300/1,530 (19.4) |
| Target vessel for the radial artery | | | |
| Left anterior descending artery system | 166/800 (20.8) | 107/467 (22.9) | 59/333 (17.7) |
| Circumflex coronary artery | 336/800 (42.0) | 259/467 (55.5) | 77/333 (23.1) |
| Right coronary artery | 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 | 813/1,428 (56.9) | 42/62 (67.7) | 771/1,366 (56.4) |
| Circumflex coronary artery system | 564/1,428 (39.5) | 16/62 (25.8) | 548/1,366 (40.1) |
| Right coronary artery system | 51/1,428 (3.6) | 4/62 (6.5) | 47/1,366 (3.4) |

Values are mean ± SD, n (%), or n/N (%). Adapted from Taggart et al. (10).
ITA = internal thoracic artery.

As a sensitivity analysis, we repeated the analysis for the first aim using the same approach.

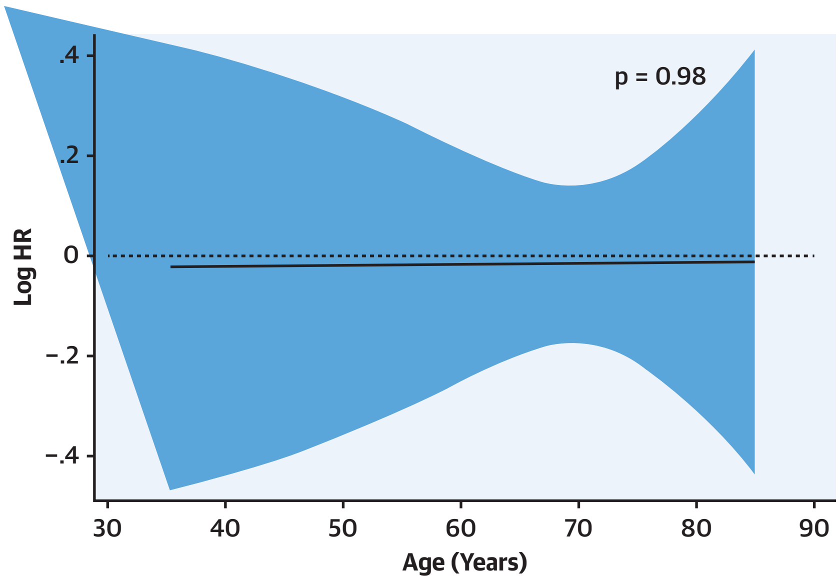
All analyses were performed using Stata version 14 (StataCorp, College Station, Texas) and SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

## 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 follow-up time was 10.00 years (quartile [Q]1 to Q3: 9.98 to 10.00 years).

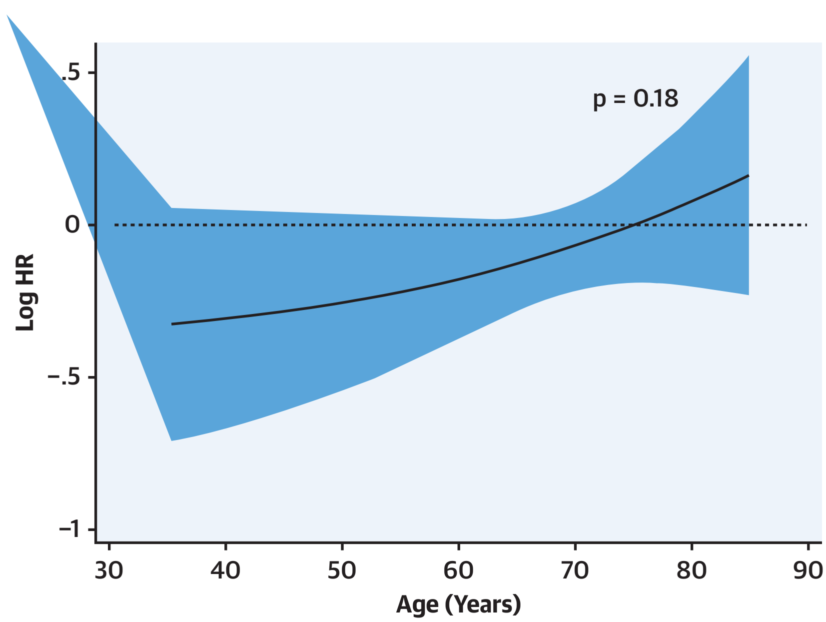
**EFFECT OF AGE ON THE OUTCOMES OF BITA VERSUS SITA GRAFTING.** For all-cause mortality (Figure 1), the logarithm of the HR of BITA relative to SITA remained close to zero across all ages, indicating no significant interaction (p = 0.98). For the composite outcome (Figure 2), a trend was noted suggesting improved outcomes for younger patients undergoing BITA compared with SITA (logarithm of HR negative for

**FIGURE 1** Treatment-Effect Plot for Interaction Between BITA Versus SITA and Age on 10-Year All-Cause Mortality



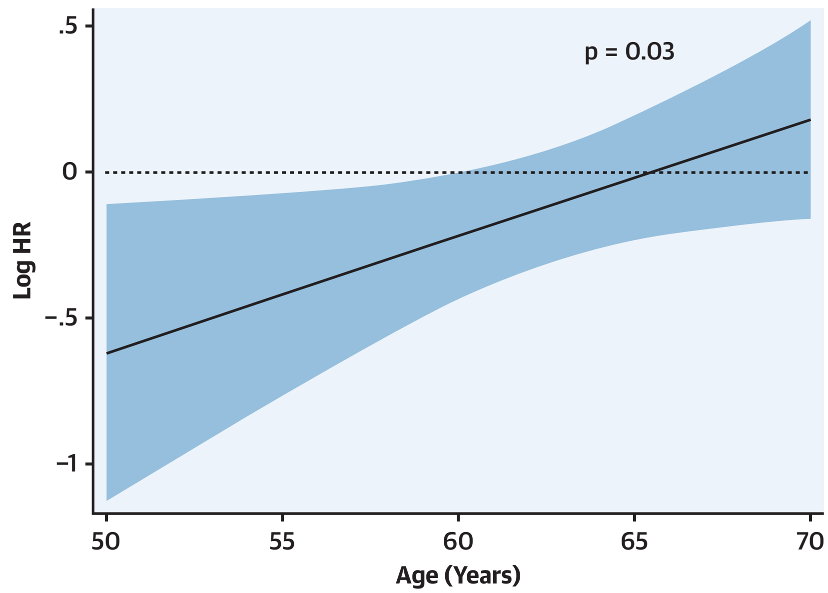

The **shading** corresponds to the 95% confidence interval for the log HR at the corresponding age. BITA = bilateral internal thoracic arteries; HR = hazard ratio; SITA = single internal thoracic artery.

**FIGURE 2** Treatment-Effect Plot for Interaction Between the 10-Year Composite Outcome of BITA Versus SITA With Age




The composite outcome includes all-cause mortality, myocardial infarction, or stroke. The **shading** corresponds to the 95% confidence interval for the log HR at the corresponding age. Abbreviations as in Figure 1.

**CENTRAL ILLUSTRATION Treatment-Effect Plot for Interaction Between the 10-Year Composite Outcome of Bilateral Internal Thoracic Arteries Versus Single Internal Thoracic Artery With Age in Patients Between Age 50 and 70 Years**

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The composite outcome includes all-cause mortality, myocardial infarction, or stroke. The **shading** corresponds to the 95% confidence interval for the log hazard ratio (HR) at the corresponding age.

younger patients and positive for older patients) consistent with the Kaplan-Meier curves for the composite outcome in the categorical analysis (Supplemental 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 ($p = 0.03$) (**Central Illustration**).

For sternal wound infection rates at 6 months (Supplemental Figure 2), the logarithm of odds ratios remained close to approximately 0.75 across all ages and there was no significant interaction with age ($p = 0.61$). Similarly, for bleeding rates (Supplemental 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 (Supplemental Figures 4 to 7).

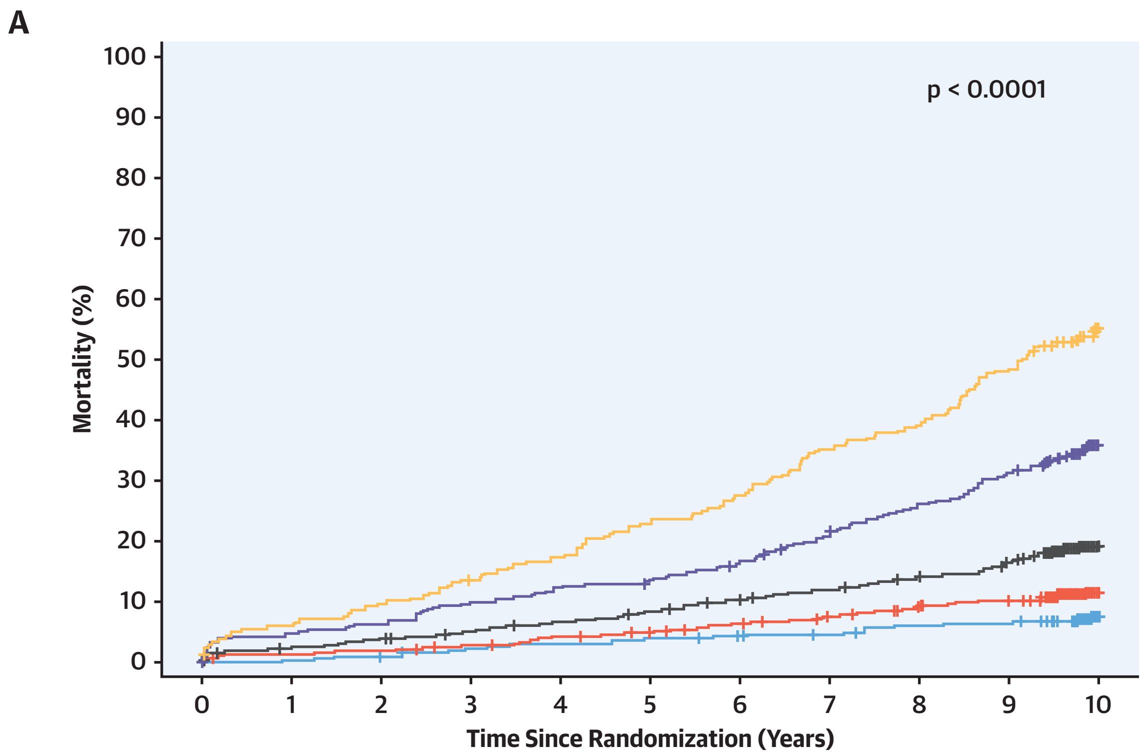
**DESCRIPTIVE ANALYSIS BY AGE GROUP.** Results for the descriptive analysis for the whole cohort divided into decades of age is summarized for all-cause mortality (**Figure 3A**), cardiac mortality (**Figure 3B**), and myocardial infarction and repeat revascularization (**Figure 3C**), respectively.

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 age >80 years subgroup. In contrast, no difference across age for the composite of nonfatal cardiac events, especially across the age 51 to 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 age 50 and 70 years, younger patients in the BITA arm had a significantly lower incidence of MAE.

**FIGURE 3** **Results for the Descriptive Analysis for the Whole Cohort Divided by Decades of Age**




| Age Groups | Number at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 - 50 | 287 | 286 | 283 | 279 | 276 | 274 | 271 | 268 | 263 | 262 | 205 |
| 51 - 60 | 910 | 893 | 886 | 877 | 862 | 853 | 839 | 823 | 808 | 790 | 596 |
| 61 - 70 | 1,200 | 1,165 | 1,147 | 1,128 | 1,109 | 1,088 | 1,063 | 1,040 | 1,013 | 983 | 696 |
| 71 - 75 | 468 | 443 | 436 | 420 | 408 | 402 | 386 | 361 | 339 | 315 | 208 |
| 76+ | 237 | 222 | 213 | 203 | 194 | 181 | 170 | 152 | 143 | 121 | 71 |

**(A)** All-cause mortality by age group. **(B)** Cumulative incidence of cardiac mortality by age group. **(C)** Cumulative incidence of myocardial infarction and repeat revascularization by age group.

*Continued on the next page*

Observational studies have suggested that the benefit of BITA grafting may be age-dependent. The increase in noncardiac mortality with increasing age and a shorter life expectancy in older patients may minimize any cardiac survival benefit gained with BITA compared with SITA. Kieser et al. (4) 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 years, but not after age 70 years (4). Similar findings were reported by Benedetto et al. (5), who found that the survival benefit of BITA was improved through age 69 years, but not afterwards. 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 with the previous observational studies, our results are based on data of higher quality and granularity that allow for better

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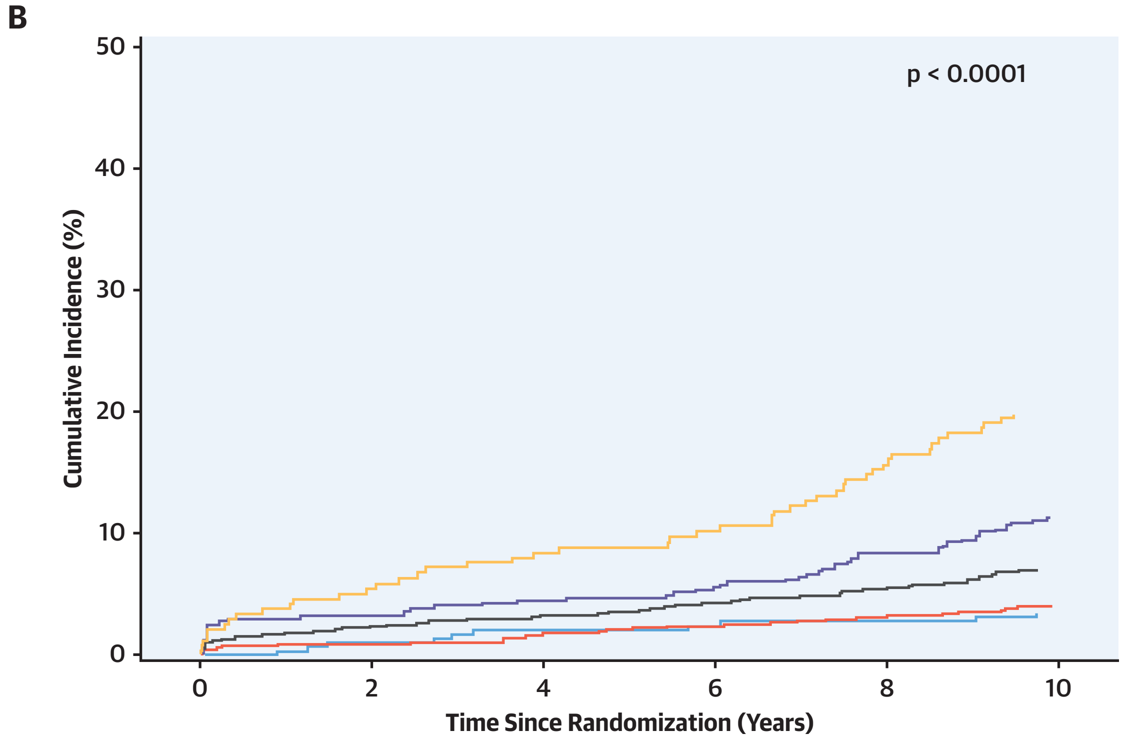
**FIGURE 3** Continued




| Age Groups | Number at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 - 50 | 287 | 286 | 283 | 279 | 276 | 275 | 271 | 268 | 263 | 262 | 205 |
| 51 - 60 | 970 | 893 | 887 | 878 | 866 | 859 | 846 | 828 | 813 | 792 | 596 |
| 61 - 70 | 1,200 | 1,165 | 1,147 | 1,129 | 1,112 | 1,093 | 1,068 | 1,045 | 1,014 | 985 | 696 |
| 71 - 75 | 468 | 443 | 436 | 422 | 410 | 405 | 389 | 362 | 340 | 316 | 209 |
| 76+ | 237 | 222 | 213 | 203 | 194 | 181 | 170 | 152 | 143 | 121 | 71 |

*Continued on the next page*

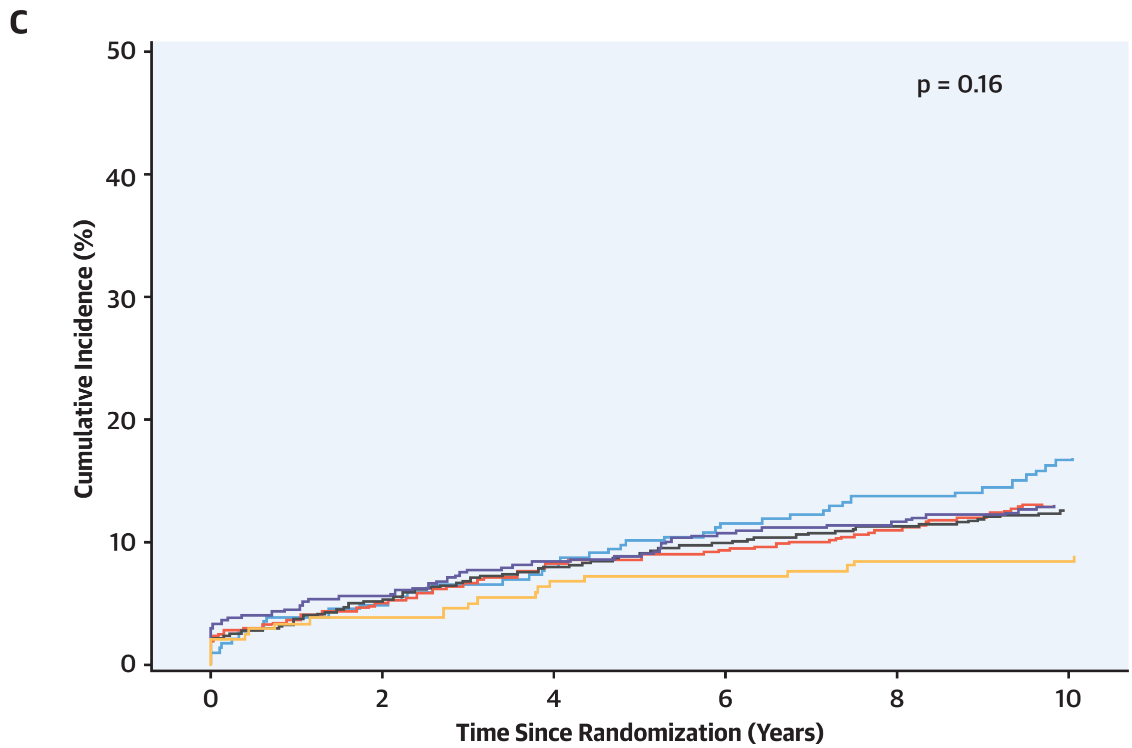
adjustment for confounders (12). However, our findings need confirmation in larger trials focused on young patients. The ROMA (Randomized comparison of the Outcome of single vs Multiple Arterial grafting) trial has an age cut-off of 70 years for patient inclusion and will provide additional important 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 noncardiac events.

Although the increase in all-cause mortality with age is expected, the increase in cardiac mortality has at least 2 possible explanations. It is possible that noncardiac 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.

**FIGURE 3** Continued




| Age Groups | Number at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 - 50 | 287 | 275 | 271 | 262 | 254 | 248 | 240 | 235 | 226 | 223 | 169 |
| 51 - 60 | 910 | 862 | 844 | 819 | 796 | 783 | 767 | 744 | 722 | 693 | 516 |
| 61 - 70 | 1,200 | 1,129 | 1,091 | 1,056 | 1,026 | 997 | 966 | 938 | 903 | 871 | 617 |
| 71 - 75 | 468 | 427 | 415 | 393 | 382 | 375 | 354 | 327 | 309 | 282 | 180 |
| 76+ | 237 | 217 | 207 | 194 | 181 | 168 | 158 | 140 | 131 | 112 | 65 |

**STUDY LIMITATIONS.** 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 3,000 patients followed for 10 years, there is limited power to explore effects of BITA and SITA grafting in subgroups. Finally, the possible role of the high crossover and cointervention rates in ART have been extensively discussed, as well as the limitations of the analysis based on the number of arterial grafts (9).

## CONCLUSIONS

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

## AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**ADDRESS FOR CORRESPONDENCE:** Dr. Mario Gaudino, Department of Cardiothoracic Surgery, Weill Cornell Medicine, 525 East 68th Street, New York, New York 10065, USA. E-mail: mfg9004@med.cornell.edu. Twitter: @WCM_CTSurgery.

## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** Younger patients exhibit more favorable long-term clinical outcomes after coronary revascularization using BITA rather than unilateral internal thoracic artery grafts.

**TRANSLATIONAL OUTLOOK:** Future trials of arterial revascularization should focus on younger patients and seek to identify other subgroups likely to gain greatest long-term benefit.

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**KEY WORDS** bilateral internal thoracic arteries, CABG, single internal thoracic artery

**APPENDIX** For an expanded Methods section and supplemental figures, please see the online version of this paper.