The Arterial Revascularization Trial: It Is What It Is

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Despite an increased emphasis for the use of bilateral internal mammary artery (BITA) grafting in coronary artery bypass graft (CABG) patients, a recent study from the Society of Thoracic Surgeons (STS) database revealed that only 4.9% of CABG patients received BITA grafts.[1] The most common reasons for not embracing BITA grafting stem from the increased risk of sternal wound complications and the quality of data from published studies comparing BITA and single internal mammary artery (SITA) grafting. The majority of data are derived from retrospective, nonrandomized studies and meta-analyses with great variability in propensity-matching leading to selection bias. Patients undergoing BITA grafting tend to be younger with fewer comorbidities. Data are lacking regarding graft patency, the quality of the vessels grafted and their Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) scores, causes of death—cardiac versus noncardiac; and compliance with Goal Directed Medical Therapy (GDMT).

Because of these deficiencies, the ART (Arterial Revascularization Trial) was initiated in 2004 to address these concerns and define the role of BITA grafting in the CABG patient.[2] This was a multicenter, prospective trial involving 3102 CABG patients in which patients were randomized to receive either BITA or SITA grafts along with GDMT. In addition, both groups received saphenous vein grafts and 21.8% of the SITA group and 19.4% of the BITA patients also received a radial artery (RA) graft. The patients were well matched with respect to age (mean=63 years), diabetes mellitus (23% of whom 5.5% were insulin dependent), sex, hypertension, smoking habits, and other comorbidities. After 10 years, there was no significant difference in mortality from any cause (20.3% BITA versus 21.2% SITA), the composite end point of death, myocardial infarction, or stroke (24.9% BITA versus 27.3% SITA) or the need for a repeat revascularization procedure (10.3% BITA versus 10.0% SITA).[3] There was, however, a significant increase in the incidence of sternal wound complications in BITA patients (3.5% BITA versus 1.9% SITA; P=0.005) and the need for sternal wound reconstruction (2.0% BITA versus 0.6% SITA; P<0.02).

Several explanations have been proposed to explain the lack of benefits of BITA grafting in the ART trial:

1. There was a high crossover rate in this trial—14% of patients assigned to the BITA group actually had a SITA.
2. 21.8% of SITA patients also received a RA graft; in essence these patients actually had multiple arterial grafting (MAG). The RA has been shown to have superior patency compared with saphenous vein grafts, which has resulted in improved long-term outcomes.[4]
3. There were no routine follow-up angiograms, so the true incidence of BITA and SITA patency was not known. In a recent study from the New York State (NYS) cardiac database, CABG patients receiving MAG versus single arterial grafts had significantly lower 7-year mortality (12.7% versus 14.3%; P<0.001).[5] This improvement in survival was not observed in patients who had undergone off-pump CABG. The incidence of off-pump CABG was 18% in the NYS series but was 40.6% in the ART trial. It is conceivable that the increased use of off-pump CABG may have resulted in decreased graft patency and contributed to the 7-year mortality in ART.
4. The sample size of ART may have been too small to show a statistically significant decrease in mortality and the composite end point of death, myocardial infarction, and stroke at 10 years. In the NYS series at 7 years, MAG patients had a significant decrease in death and major adverse cardiovascular events.[5] However, the sample size in the NYS series was 3 times greater than in ART.
5. Adherence to GDMT was extremely high in ART. GDMT is underutilized in CABG patients and was achieved in only 50% of patients 5 years following surgery.[6–8] Compliance with GDMT after CABG has been reported to be as low as 23% for angiotensin-converting enzyme inhibitors, 28% for statins, and only 70% for aspirin.[9,10] In ART, after 10 years, compliance with angiotensin-converting enzyme inhibitors was 71%, 90% for statins, 81% for aspirin, and 74% for β-

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blockers.[3] Noncompliance with GDMT after CABG has been found to decrease long-term survival, freedom from myocardial infarctions, and the need for repeat coronary revascularization procedures.[8,11]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Gaudino and coauthors provide another explanation for the failure of ART to show superiority for BITA grafting.[12] They performed propensity matching from selected observational and meta-analysis studies involving SITA and BITA patients and found that the 10-year survival of the SITA arm of ART was significantly higher than that of the matched observational studies and that the 10-year survival of the BITA arm was significantly lower. They concluded that the improved outcomes of SITA patients and the decreased outcomes of BITA patients in ART may have contributed to the lack of superiority of BITA grafting in this trial. There are, however, several important limitations in this analysis. A table comparing the risk profiles of the patients in ART with those of the matched studies would have been helpful to determine whether the comorbidities of the patients in these 2 cohorts were similar. Important data such as the completeness of revascularization, STS Predicted Risk Of Mortality (PROM) scores, the incidence of diabetes mellitus and insulin-dependent patients, smoking habits, NYHA Class, and the urgency of surgery were not provided. No mention is made of the percentage of patients who were adherent to GDMT or the percentage of patients who received RA grafting. Important long-term data such as the cause of death (cardiac versus noncardiac), the incidence of myocardial infarctions, strokes, and the need for repeat revascularization are not provided.

Another explanation for the lack of superiority for BITA grafting in the ART trial may be that not all CABG patients will benefit from BITA grafting. When determining which CABG patients will benefit the most from BITA grafting, the following factors should be taken into consideration:

1. Age—Lytle et al first showed that improved BITA grafting was seen only after 10 years.[13] In the NYS series, the survival advantage for MAG was seen after 7 years and in ART, the survival curves began to diverge to show a nonsignificant advantage from BITA grafting after 7 years. Therefore, CABG patients undergoing BITA should have a life expectancy of at least 7 to 10 years. The NYS series and other series showed increased survival with BITA or MAG only in patients younger than 70 years[5,14,15] and in some series, younger than 65 years.[16,17]
2. Comorbidities—Patients with comorbidities that result in limited life expectancy, such as end stage renal disease, active smoking, peripheral vascular disease, uncontrolled or insulin-dependent diabetes mellitus, and those with underlying malignancies are also unlikely to benefit from BITA grafting.
3. Incomplete Revascularization—The inability to achieve complete revascularization in CABG patients may be because of irreversibly damaged myocardium, and small and diffusely diseased distal target vessels. Schwann et al have shown that incomplete revascularization is associated with decreased long-term survival following CABG despite the use of BITA and MAG.[18]
4. Sternal Issues—In both the ART and NYS series, the incidence of sternal wound complications was significantly higher in patients with BITA grafting.[2,3,5] Patients at risk for sternal complications such as obese patients, diabetic females on insulin, frail patients with osteoporosis, patients with chest wall deformities, those on steroids, and heavy smokers with chronic obstructive pulmonary disease are all at risk for sternal wound complications, and in whom BITA grafting should be avoided.
5. Distal Target Vessel Stenosis—The degree of distal target vessel stenosis is also an important factor in determining the suitability for BITA and MAG. All ITA grafts have decreased patency in vessels with <70% stenosis, while RA grafting is best for patients with at least an 80% stenosis.

Finally, although ART failed to show the superiority of BITA versus SITA grafting after 10 years, it should not be considered a "failed" study. In fact, it is a "landmark" trial. The real conclusion from ART is that when RA grafts and GDMT are performed in conjunction with SITA grafting, the overall results are equivalent to what can be obtained with BITA grafting, without the increased risk of sternal wound complications that contribute to increased morbidity and mortality. Furthermore, ART highlights the importance of GDMT to optimize the short- and long-term outcomes following CABG. Rather than attempting to explain the reasons for the shortcomings of ART, the authors should be encouraged to continue to analyze the ART data to determine which subgroups of patients will derive the greatest benefits from BITA grafting.

Disclosures

None.

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