Has Arterial Revascularization Trial [ART] burst the BITA bubble?

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Abstract

The 10-year outcome of the Arterial Revascularization Trial (ART) has recently been published. The study is the largest randomized study comparing bilateral internal thoracic artery (BITA) with single internal thoracic artery (SITA) as a grafting strategy for coronary artery bypass. In this review, a critical appraisal of the study has been performed where the result of the trial has been discussed along with the risk of sternal wound infections, the presence of a learning curve, and the influence of volume on outcomes. The influence of BITA grafting on other aspects like influence on hospital stay and quality of life outcomes has also been discussed.

Keywords BITA · ART · CABG

Even though BITA grafting was shown to be superior to SITA almost two decades back [1], the uptake of BITA grafting has remained very low (4% in the USA) [2]. Studies carried out to identify barriers behind the low uptake found that the existence of a learning curve and perception of increased sternal wound problems were the main concerns over BITA grafting [3]. Also, the superiority of BITA was only from non-randomized propensity-based studies and meta-analysis of observational studies [4]. This led to the Arterial Revascularization Trial (ART), the largest randomized trial in cardiac surgery comparing BITA versus SITA.

ART was an unblinded multicenter, randomized controlled trial (RCT), conducted in 28 hospitals in seven countries, with patients randomized to SITA ($n = 1554$) or BITA ($n = 1558$) grafts. The study included expert surgeons who had performed at least 50 BITA grafting. Apart from the primary objective of survival and the need for re-interventions at 10 years, the secondary outcome measures included clinical events and quality of life (QoL) and health economic assessments [5].

Before evaluating the trial, certain facts need highlighting. Firstly, 28% of the patients who met the eligibility criteria were actually randomized [5]. Secondly, despite having the

highest 10-year follow-up in recent times, there was no information on ITU and hospital length of stay in 226 (7.3%) patients and at 10 years, we did not know whether 71 (2.3%) patients participating in the trial were dead or alive [6]. The total attrition was 5.1% (159) if withdrawal from the trial is also included. Information was also incomplete in 279 (9%) patients regarding incidence of myocardial infarction, stroke, and repeat revascularization [7]. It has to be stressed that both mortality and re-intervention were the primary outcomes of the study. Moreover, a study that was meant to provide the most compelling data on BITA usage, the technique of harvesting (pedicled or skeletonized), was not documented in one-third of the patients (1046 out of 3102) [8].

The information obtained from the trial can probably be best appreciated in the context of the questions this study was expected to answer.

Does BITA grafting lead to increased survival and decreased risk of re-intervention?

The study analyzed trial data in three different ways:

1. Intention to treat (the most robust way of analyzing results from a RCT, however, some of the patients randomized as BITA may actually have received SITA).
2. As per protocol (comparison based on patients who actually received the randomly assigned treatment).

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3. As treated (this group compared patients who had multiple (≥ 2) arterial grafts versus those who received only one arterial graft).

At 10 years, in intention-to-treat analyses, there were no significant differences in all-cause mortality or in the rate of composite outcome of death, myocardial infarction, or stroke. The rate of repeat revascularization was also similar (10.3% in the BITA group vs. 10.0% in the SITA group). The composite outcome of death from any cause, myocardial infarction, or stroke was 24.9% in the BITA group vs. 27.3% in the SITA group [9]. There was also little difference between the BITA and SITA groups in QoL at 12 months as measured using the shortened WHO Rose angina questionnaire or the EuroQol EQ-5D [5].

Even when the analysis was done “as per protocol” and thus provided a direct comparison between BITA and SITA, there was no difference in 10-year survival [6]. This could well be due to non-adherence to the randomly assigned treatment resulting in a loss of statistical power, use of radial-artery grafts in the SITA group serving as a confounder, and an exceptionally high rate of guideline-directed medical therapy further narrowing the differences in clinical outcome between the two groups.

The only difference in survival was seen in the “as treated” analysis when patients receiving two or more arterial grafts were compared with those receiving single arterial graft. At 10 years, the mortality in multiple arterial grafts group was 18.6% versus 23.1% in the single arterial group (adjusted hazard ratio 0.81).

Does BITA harvesting increase the rate of sternal wound infections?

It is clear from the trial that both the incidence of sternal wound infections and sternal wound reconstruction were significantly higher in the BITA group when the analysis was done on an intention to treat basis.

Both sternal wound infection (54 (3.5%) vs. 30 (1.9%), $p = 0.005$) and sternal wound reconstruction (29 (1.9%) vs. 9 (0.6%), $p = 0.002$) were significantly higher in the BITA group compared to the SITA group [5, 7].

The authors mention that almost half the patients in each group who required sternal wound reconstruction were diabetics. However, it is apparent from the data that even in non-diabetics, sternal reconstruction was required in 4 (out of 1191) patients in the SITA group as opposed to 15 (out of 1177) in the BITA group [5]. This was statistically significant and therefore the risk of sternal wound reconstruction remains high in both diabetics and non-diabetics after BITA grafting.

In 2056 patients (out of 3102) where the technique of ITA harvesting (pedicled or skeletonized) was documented, it was

shown that pedicled BITA (but not skeletonized BITA) was associated with a significantly increased risk (two times) of any sternal wound complications when compared with pedicled SITA. The authors have, in fact, concluded that the detrimental effect of pedicled BITA on the incidence of any sternal wound complication is exaggerated in diabetics on insulin. However, it remains significantly associated with a higher risk of sternal wound complications even in non-diabetics. Pedicled BITA was found to significantly increase the risk of sternal wound complication in both obese as well as non-obese patients [8].

Does BITA harvesting have a steep learning curve?

The trial throws some very interesting facts. In the SITA group, 3.4% did not receive a single ITA and 14% of the patients who had been randomly assigned to the BITA group actually received a single ITA [5, 7].

In itself, these numbers may not be of concern. But when seen against the backdrop of the inclusion of “expert surgeons” participating in the trial, the cross-over rate of 14% from BITA to SITA questions the degree of expertise required for carrying out BITA grafting. The trial stipulated that “Only surgeons with experience of 50 BIMA operations were able to undertake BIMA procedures in the trial” [5]. Clearly, this is not sufficient experience as the cross-over rate (BITA to SITA) in the study was as high as 100% for some surgeons and up to 49% for certain centers [5, 9]. Surgeons who performed < 50 BITA procedures in the trial setting (not total experience) had the highest conversion rate from BITA to SITA. The reasons for patients not getting the allocated treatment have been detailed in the 1-year report of the ART trial and included unsuitable vessel due to size or condition, patient status, surgeon preference, and unsuitable coronary anatomy [5]. Also, while in the hands of surgeons performing ≥ 50 operations in the trial, the 10-year mortality after BITA grafting was lower at 19.9% compared with 25.1% after SITA, among surgeons who performed < 50 operations in the trial the mortality with BITA was higher (20.8%) compared with SITA (17.9%). So, the concerns surgeons have had in the past about the technical complexity of the procedure seem real and have been confirmed by the trial. This barrier is certainly not insurmountable for cardiac surgeons but equally the learning curve of this procedure cannot be underplayed.

Does BITA harvesting increase the operating time, length of stay, and cost?

The effect of BITA grafting on timing was minimal with BITA grafting adding on an average 23 min to the duration of

operation and 105 min to the duration of mechanical ventilation [5]. However, at 12 months from randomization, mean costs were approximately 9% higher ($p = 0.002$) in the BITA group compared with the SITA patients primarily due to longer time in theater and in-hospital stay and slightly higher costs related to sternal wound problems during follow-up [10].

To summarize the much awaited and the most authoritative trial on the subject, the Arterial Revascularization Trial has shown that BITA is not superior to SITA at least in the first decade following CABG. It may be possible that at further follow-up (at 15 or perhaps 20 years), a better survival of the BITA group may become apparent but until that time, SITA appears to be an equally good option. However, in expert hands when multiple arterial grafting (≥ 2) was performed, there was a definite survival advantage compared with single arterial grafting, a finding that will be more extensively examined in the ROMA (randomized comparison of the clinical outcome of single versus multiple arterial grafts) trial. The study clearly demonstrates the increased risk of sternal wound problems with the use of pedicled BITA especially in those at higher risk, such as insulin-dependent diabetic individuals, women, and those with increased body mass index. Apart from sternal wound concerns, the study confirms the technical complexity of the procedure and the presence of a steep learning curve, both of which have prevented the widespread adoption of the technique. These issues, along with the absence of overwhelming survival advantage, makes one wonder if the study will encourage greater adoption of BITA grafting.

Compliance with ethical standards

The manuscript does not mention any patient or patient details and hence formal ethical approval is not required.

Conflict of interest The author declares that he has no conflict of interest.

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