Lessons from the arterial revascularization trial

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The arterial revascularization trial (ART)

Trial description

Single internal mammary artery (SIMA) + other (saphenous vein and/or radial artery) Versus bilateral IMA +/– other.

Primary outcome: overall 10-year survival.

Secondary outcomes: (I) clinical events (including and not limited to cause of death, revascularization, myocardial infarction, stroke); (II) quality of life; (III) costs of care.

Prescribed subgroup analyses: age, diabetes, left ventricular function, off pump, type of non-IMA grafts, number of grafts.

Randomized 3,102 patients from June 2004 to December 2007.

Mid-term outcomes

The 5-year mid-term outcomes of the Arterial Revascularisation Trial (ART) did not show a survival benefit for bilateral internal mammary artery grafting (BIMA) over single internal mammary artery grafting (SIMA) for multi-vessel coronary disease. The survival curves over 5 years were almost identical such that it seems unlikely that a significant difference in the primary end point of 10 year survival will be achieved (1). This finding is a disappointment to the minority of surgeons who routinely use BIMA and will provide some validation to those who use SIMA, particularly those who augment the SIMA with a radial artery graft. Accordingly, these mid-term findings are unlikely to change current practice trends as those surgeons who uncommonly use BIMA will not increase their usage and those surgeons who routinely use BIMA will continue to follow the powerful observational studies have been published in support of BIMA (2) since the conception of ART 13 years ago. The mid-term outcomes did show a much higher usage of aspirin, beta blockers and angiotensin inhibitors than has been seen in previous studies and probably demonstrates a world-wide evolutionary change. This high level of compliance was seen in both arms of the trial but will likely provide greater benefit to patients with multiple vein grafts.

Reasons for the ART

The first major observational study of BIMA versus SIMA was from the Cleveland Clinic published in 1999 (3). For those surgeons using BIMA at that time, it was "a long time comin" and validated the practice. For the majority of surgeons, the 3% absolute survival benefit at 15 years simply was not enough regardless of the hazard ratio and P value. The revision of this 15 year survival benefit to 9% in propensity matching and larger numbers in 2004 (4) was still unconvincing for the majority of surgeons. In particular, the evidence from other studies relating to the optimum types of arterial grafts and configurations was then, and still is confusing (5).

Early results

The USA has the lowest uptake of BIMA use presumably due to the increased costs associated with the higher risk of sternal wound complications in a health care system that is very cost sensitive. The overall comparative cost analysis is

one of the secondary outcomes of the ART but no interim analyses have been published. The incidence of sternal complications continues to decrease and the management thereof continues to improve, providing reduced morbidity and substantial cost savings over historical experiences. Subgroup analyses from ART showed that the risk of any sternal wound complication was the same for SIMA pedicled harvest as it was for BIMA skeletonized harvest (OR =1.00, 95% CI: 0.65–1.53). The risk was lowest for SIMA skeletonized harvest and the difference between SIMA and BIMA harvesting was smaller both absolutely and relatively with skeletonization (6). The use of limited right IMA harvesting for composite graft use and harmonic harvesting might further reduce sternal wound complications. The ART analysis was for any sternal wound complication within 1 year of surgery. The numbers of sternal reconstructions were too low for meaningful subgroup analyses to be performed but there was no suggestion of a trend towards reduced sternal reconstruction rates with skeletonized harvesting. Unfortunately, over one third of patients had insufficient data on harvest technique to be included in the analyses. The 1 year outcomes analyses of the total cohort showed longer operative times, time in intensive care and duration of hospital stay for the BIMA group (7). Subgroup analyses for the impact of harvest technique on these outcomes were not performed. Although the ART has shown that skeletonized BIMA harvesting is associated with a reduced risk of any sternal wound complication, no evidence has been presented to suggest that this will reduce the overall costs of patient care.

ART and others

The other trial of BIMA versus SIMA is the Radial Artery Patency and Clinical Outcomes (RAPCO) trial which commenced recruiting in 1996 (8). The analysis of the 10-year outcomes is currently in the process of publication and should be available soon. In this study a radial artery was used as the second conduit in the SIMA group. There was no survival difference in the mid-term analysis at a mean follow up of 6 years, nor was there any difference in graft patency. The ART allows use of the radial artery or saphenous vein with analysis of these sub-groups as a secondary end point. However, radial artery patency rates approaching those of the right IMA at 10 years are likely to reduce the impact of the primary outcome (9). The multiple subgroup analyses prescribed in the ART protocol as secondary end points will provide much useful information regardless of the significance of the primary end point. Although the survival curves are very similar at 5 years, it should be noted that the attrition rate for IMA grafts is highest in the first 5 years (10) and for vein grafts it is highest in the second and third 5 year periods.

A 20-year follow up of patients under the age of 40 years who underwent predominantly saphenous vein only coronary surgery, showed a 27% mortality rate at 10 years. Of those who survived the first 10 years, an estimated mortality of 69% occurred during the second 10 years while the patients were still less than 60 years old (11). Although this horrendous mortality predated the routine use of aspirin, statins and angiotensin inhibitors, the study emphasises the great benefit of IMA grafting during the second 10 years, particularly in younger patients (4). It would be logical for the ART trial to be extended to 15 years for collection of survival data only, as observational studies have shown increasing divergence of the survival curves during the second 10 years (4).

ART limitations

Completion of the 10 year follow up period for all patients will occur in December this year. It is hoped that some useful analyses will be published next year. These analyses should take into account the limitations encountered so far throughout the study as follows.

Treatment crossover

Overall, 8.4% of randomized patients received the opposite therapy and a further 2% received neither SIMA nor BIMA. This is similar to the 7.3% protocol failure rate in the RAPCO trial (8). In the ART, there was a 16% failure to perform BIMA and a 4% failure to perform SIMA such that the treatment given groups were BIMA n=1,332 and SIMA n=1,709. The late survival analyses will be performed on these "as treated" groups as well as the intention to treat groups. The overall 5-year mortality for the as treated groups was 8.4% (SIMA=8.7%, BIMA=8.0%) and the expected 10 year mortality for the trial design was 22% with a 5% difference between groups. However, with minimal divergence of survival curves at 5 years, the absolute survival difference will likely need to exceed 5% for a log rank comparison to reach significance.

Graft deployment

The protocol stipulated the deployment of both IMAs to the left coronary system in the BIMA group. In patients

with multi-vessel disease involving the LAD, the second most important coronary artery has been judged by the attending surgeon to be part of the right coronary system in 27% of patients (3). It is assumed that patients with double vessel disease involving the left anterior descending and right coronary arteries should have been excluded from randomization. Therefore, it is estimated that the second IMA has been applied to the third most important coronary artery in approximately 20% of BIMA cases. The inclusion of this variable in the analyses has not been stated in the protocol.

Radial artery use

The radial artery was used in 21% of the coronary surgery ART cohort with similar rates in the intention to treat groups. The analysis in the as treated groups was not provided but the use of a second arterial graft in the more than 20% of the SIMA patients is likely to benefit this group (9). The subgroups of radial artery use will be analysed as part of the secondary outcomes analyses.

In summary, the ART is the largest ever randomized trial of coronary surgery patients. Analyses for both primary and secondary outcomes are likely to provide substantial amounts of information which will help to guide future practice. The difficulties in running a large multi-centre randomized trial over 13 years are apparent but the data acquired and analyses provided are extremely sound. The limited number of exclusions allows a wider range of variables which will be appropriately analysed as secondary outcomes. A significant primary outcome may or may not be achieved at 10 years but the potential for a post hoc analysis at 15 years should exist. The secondary outcomes analyses will be important. We are still awaiting the results.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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