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Bilateral versus single internal thoracic coronary artery bypass grafting: the ART RCT

Marcus Flather, Arnaldo Dimagli, Umberto Benedetto, Belinda Lees, Alastair Gray, Stephen Gerry, Ajita Naik, Jo Cook, Mario Gaudino, Matthew Little and David P Taggart; on behalf of the ART Investigators

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Bilateral versus single internal thoracic coronary artery bypass grafting: the ART RCT

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Abstract

Bilateral versus single internal thoracic coronary artery bypass grafting: the ART RCT

Marcus Flather,[1*] Arnaldo Dimagli,[2,3] Umberto Benedetto,[2] Belinda Lees,[4] Alastair Gray,[5] Stephen Gerry,[6] Ajita Naik,[3] Jo Cook,[7] Mario Gaudino,[3] Matthew Little[5] and David P Taggart[4]; on behalf of the ART Investigators

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Background: There is debate whether the use of more arterial grafts during coronary artery bypass graft surgery provides advantages to the standard operation using the left internal thoracic artery plus vein grafts. We review data from the Arterial Revascularisation Trial to determine whether there is support for the multiple arterial graft hypothesis.

Methods: Patients undergoing coronary artery bypass graft for clinical reasons and who provided written informed consent were randomised to standard coronary artery bypass graft using the single internal thoracic artery or use of bilateral internal thoracic arteries. Additional vein grafts could be used. The primary outcome was all-cause mortality at 10 years and exploratory analyses were carried out to test the multiple arterial graft hypothesis.

Results: A total of 3102 patients were enrolled (1548 bilateral internal thoracic artery and 1554 single internal thoracic artery). Follow-up to 10 years for vital status was 98% complete. In the bilateral group, 14% of patients received a single internal thoracic artery only and use of radial artery grafts occurred in about 20% of patients in both groups. Aspirin was used in 81% of the patients, beta-blockers in 74%, statins in 90% and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 73%. At 10 years, death rates were 20.3% and 21.2% in the bilateral internal thoracic artery and single internal thoracic artery groups, respectively (hazard ratio 0.96, 95% confidence intervals 0.82 to 1.12; $p = 0.62$) and composite of all-cause mortality, myocardial infarction or stroke 24.9% and 27.3%, respectively (hazard ratio 0.90, 95% confidence interval 0.79 to 1.03; $p = 0.12$). Exploratory analyses using the 'as-treated' approach indicate that outcomes were better in patients who received multiple arterial grafts (adding the right internal thoracic and/or radial arteries) compared with a single arterial graft. This effect appeared to be greater in patients with diabetes and those aged 70 years or less. Use of total arterial grafting without vein grafts may provide the best outcomes.

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Limitations: The elevated cross-over rate between bilateral internal thoracic artery and single internal thoracic artery and the non-randomised use of radial artery grafts may have contributed to a loss of power to detect a difference in mortality between the two groups. Moreover, secondary analyses are prone to bias as they compare non-randomised groups.

Conclusions: The Arterial Revascularisation Trial is one of the largest long-term studies in cardiac surgery. The primary analysis did not show a mortality benefit for bilateral internal thoracic artery at 10 years, perhaps due to high crossover rates in the bilateral internal thoracic artery group and concomitant use of the radial artery. Secondary analyses suggest a mortality benefit for patients receiving multiple arterial grafts compared with single arterial graft with possible greater effects in patients with diabetes and separately in patients aged 70 years or above. The trial will follow patients to 15 years and the continuing Randomized Comparison of the Clinical Outcome of Single versus Multiple Arterial Grafts trial will further test the multiple arterial graft hypothesis.

Trial registration: This trial is registered as ISRCTN46552265.

Funding: This project was funded by the British Heart Foundation, the UK. Medical Research Council and the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation programme and will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 10, No. 7. See the NIHR Journals Library website for further project information.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/JYGF5402).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

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List of abbreviations

ART	Arterial Revascularisation Trial
BITA	bilateral internal thoracic artery
CABG	coronary artery bypass graft
CAD	coronary artery disease
CI	confidence interval
CT	computed tomography
DSWI	deep sternal wound infection
HR	hazard ratio
ITA	internal thoracic artery
LITA	left internal thoracic artery
MAG	multiple arterial graft
MI	myocardial infarction
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
RA	radial artery
RITA	right internal thoracic artery
ROMA	Randomized Comparison of the Clinical Outcome of Single versus Multiple Arterial Grafts
SAG	single arterial graft
SITA	single internal thoracic artery
SVG	saphenous vein graft
TAG	total arterial graft

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Plain language summary

Introduction

Coronary artery bypass grafting is a surgical procedure aimed at improving blood flow in narrowed or blocked coronary (heart) arteries. The cardiac surgeon typically uses an artery from inside the chest wall (the internal thoracic artery) and veins from the leg to bypass the effected coronary arteries. Growing evidence suggests that using two internal thoracic arteries may be better than one. The main question in the Arterial Revascularisation Trial was 'would the use of two internal thoracic arteries allow patients to live longer after coronary artery bypass graft than those who received a single internal thoracic artery?'

Methods

The Arterial Revascularisation Trial was carried out in 28 hospitals in 7 countries. Patients scheduled to have coronary artery bypass graft and willing to participate in the trial were allocated at random (like tossing a coin) to grafting with either a single or a double internal thoracic artery. Additional vein or arterial grafts were used as considered necessary for that patient. Patients enrolled into the Arterial Revascularisation Trial were then followed-up for 10 years.

Results

A total of 3102 patients were enrolled in the trial; 1548 received bilateral internal thoracic artery and 1554 single internal thoracic artery grafts. Ninety-eight per cent of the patients were followed-up for up to 10 years and no statistical difference in survival was detected between the two groups at this timepoint (20.3% in the bilateral group vs. 21.2% in the single internal thoracic artery group). Additional analyses suggested that using more than one arterial graft, including the radial artery (from the arm), compared with using a single arterial graft, may be better, but this needs to be confirmed by further research.

Limitations

Some patients received a single internal thoracic artery when they should have received bilateral internal thoracic arteries, which could have reduced the efficiency of the trial to detect a difference between the two groups.

Discussion

The Arterial Revascularisation Trial is one of the largest long-term studies in cardiac surgery. This trial did not show that using two internal thoracic arteries during coronary artery bypass graft provides better outcomes for patients than using a single internal thoracic artery. Further results from the trial will be released upon completion of follow-up at 15 years.

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Scientific summary

Objectives

The Arterial Revascularisation Trial (ART) was a superiority trial aimed at comparing the outcomes of patients undergoing coronary artery bypass grafting (CABG) with either a bilateral internal thoracic artery (BITA) or single internal thoracic artery (SITA). The main secondary questions were whether using multiple arterial grafting (MAG) was associated with improved clinical outcomes and whether additional factors influence the efficacy of MAG such as diabetes and age.

Methods

Patients with multivessel coronary artery disease (CAD) involving at least the left anterior descending artery and the circumflex artery undergoing CABG were included and randomised equally to BITA or SITA. Emergency patients (refractory myocardial ischaemia/cardiogenic shock) and those requiring single grafts or redo CABG were excluded. After surgery, patients were followed-up on annual basis. Based on power calculation, 2928 patients were needed to be enrolled to detect an absolute 5% difference in mortality between the two groups with 90% power at the 5% significance level.

The primary outcome of the trial was all-cause mortality and the secondary outcomes were the composite of death from any cause, myocardial infarction (MI), or stroke (in a time-to-event analysis), rate of repeat revascularisation and safety outcomes (including bleeding and sternal wound complications).

The primary research question used the log rank method to compare survival in the BITA and SITA groups based on the intention to treat principle and censored patients at 10 years of follow-up after the date of randomisation. Secondary analyses used the as-treated principle and applied propensity score-based methods as appropriate to reduce confounding.

Results

A total of 3102 patients were enrolled in the trial: 1548 received BITA and 1554 SITA. Complete follow-up data for the primary outcome were available for 98% of patients at 10 years. Aspirin was used in 80%, beta-blockers 74%, statins 90% and angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers in 71%. The death rate at 10 years was 20.3% in the BITA group and 21.2% in the SITA group [hazard ratio (HR) 0.96; 95% confidence interval (CI) 0.82 to 1.12; $p = 0.62$] while the composite of all-cause mortality, MI or stroke occurred in 24.9% in BITA compared with 27.3% in SITA (HR 0.97; 95% CI 0.83 to 1.14; $p = 0.12$). In those randomised to BITA, 86% actually received BITA grafts while in the SITA group, 97.5% received SITA. Additional radial artery grafts were used in 19% of patients in BITA and 22% in SITA.

In a secondary analysis exploring the effect of multiple (MAG) and total arterial grafting (TAG), there was a significant trend toward a reduction in 10-year mortality in the MAG and TAG groups compared with single arterial grafting (SAG) (test for trend = 0.04). TAG was associated with a reduction in all-cause death when compared with SAG ($P = 0.03$). The benefit of TAG was also confirmed for the composite endpoint including death, MI, stroke or repeat revascularisation ($P = 0.02$) compared with SAG.

When investigating the effect of diabetes, MAG was associated with a survival benefit in both the diabetic and non-diabetic groups compared with SAG. Similarly, MAG was associated with lower rates of

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the composite endpoint of death, MI and stroke in the diabetic and non-diabetic groups. However, MAG was associated with higher rates of deep sternal wound infection compared with SAG in both the diabetic and non-diabetic groups. Patients with insulin-dependent diabetes receiving MAG experienced the highest absolute rate of sternal wound infection (9.6%). Use of BITA was found to be associated with higher rates of sternal wound infection.

Limitations

The elevated crossover rate between BITA and SITA and the non-randomised use of RA grafts may have contributed to a loss of power to detect a difference in mortality between the two groups. Moreover, secondary analyses are prone to bias as they compare non-randomised groups.

Conclusions

The ART has shown that is possible to run pragmatic long-term trials in cardiac surgery. Overall, the study has not shown that use of BITA is associated with reduced mortality compared to SITA. Secondary analyses support the potential benefit of MAG and TAG. More information is needed to understand the interaction of graft patency and clinical outcomes after CABG, and routine computed tomography coronary angiography may be a useful option.

Trial registration

This trial is registered as ISRCTN46552265.

Funding

This project was funded by the British Heart Foundation, the UK Medical Research Council and the National Institute of Health and Care Research (NIHR) Efficacy and Mechanism Evaluation programme and will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 10, No. 7. See the NIHR Journals Library website for further project information.

Introduction

Coronary artery disease (CAD) is one of the most common causes of premature death and disability globally and its impact is increasing over time.[1] Coronary revascularisation with percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery are generally reserved for patients with more advanced symptomatic CAD. There is considerable evidence that PCI and CABG improve symptoms and in targeted populations improve clinical outcomes such as risk of death and myocardial infarction (MI).[2,3] CABG is one of the most common major surgical procedures performed worldwide and, given its cost and potential morbidity for patients, it is important to understand optimal methods that provide the best outcomes in different populations.

The standard CABG procedure is to anastomose the left internal thoracic artery (LITA) to the left anterior descending coronary artery and to use aortocoronary saphenous vein grafts (SVG) to bypass other narrowed segments in circumflex and right coronary arteries. This procedure has been established based mainly on observational evidence but is associated with good short- and long-term outcomes.[4–6] The CABG pooling project analysed several randomised trials of CABG compared with medical therapy from the 1980s and 1990s and showed generally better mortality outcomes for CABG, especially in those with left ventricular dysfunction and those with advanced coronary disease.[7] Multiple trials comparing PCI with CABG have shown that CABG has superior mortality outcomes compared with PCI in patients with advanced coronary disease and especially those with diabetes.[8–11]

Multiple arterial grafts (MAG) may offer better outcomes due to better long-term patency rates compared with vein grafts after CABG.[12] The right internal thoracic artery (RITA) and the radial artery (RA) are the most common additional arterial conduits to the LITA and observational studies have shown that MAG is associated with lower mortality than standard LITA plus SVG.[13–15] The MAG hypothesis has wide support and has been extended to include the total arterial graft (TAG) hypothesis where CABG is only carried out using arterial grafts. In this report, we analyse the efficacy of the MAG hypothesis in the Arterial Revascularisation Trial (ART),[16] one of the largest and longest-running randomised CABG trials.

Arterial Revascularisation Trial methods

Trial design

The primary research question in ART is whether routine use of bilateral internal thoracic arteries (BITA) provides better mortality outcomes at 10 years compared with a single internal thoracic artery graft (SITA) for patients undergoing CABG for the management of symptomatic CAD.[17] For this report, the main secondary questions are whether MAG (whether provided by the RITA and/or RA) are associated with improved mortality or the composite of death, MI or stroke and whether additional factors influence the efficacy of MAG such as diabetes and age.

ART is a two-arm randomised multicentre trial conducted in 28 hospitals in 7 countries. The trial complies with the Declaration of Helsinki and commenced after ethical approval was obtained in all participating centres. The study is sponsored by the University of Oxford, with funding from the British Heart Foundation, the UK Medical Research Council and the National Institute of Health Research Efficacy and Mechanism Evaluation (England). Trial coordination was provided initially by the Clinical Trials and Evaluation Unit at the Royal Brompton and Harefield NHS Foundation Trust in London, and from 2014 by the Surgical Intervention Trials Unit, University of Oxford.

Patients, enrolment and randomisation

Eligible patients were those with multivessel CAD scheduled to undergo CABG (including patients requiring urgent surgery, but not those with evolving MI). Those requiring only single grafts or concomitant valve surgery, as well as those with a history of previous CABG, were excluded. Each

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patient was required to provide written informed consent. Patients were randomised by telephone to the coordinating centre in a one-to-one ratio to BITA or SITA grafting. The randomisation sequence was generated with randomly varying block sizes and stratified by centre. To reduce the possibility of outcome events occurring between randomisation and revascularisation, it was recommended that surgery be performed within six weeks of randomisation. It was calculated that 2928 patients would need to be enrolled to detect an expected difference of 5% in mortality at 10 years with 90% power at the 5% significance level. The aim was to enrol 3000 patients (1500 in each group) over a recruitment period of 2–3 years and to follow them for 10 years.[17]

Surgical procedure

The BITA graft group received both LITA and RITA grafts to the two most important left-sided coronary arteries with supplemental vein or RA grafts to other coronary arteries as clinically indicated. In the BITA group, internal thoracic artery (ITA) grafts could be used as composite grafts to each other, as long as one remained in situ. Anastomosis of an ITA graft to the right coronary artery was not permitted because of concerns of inferior long-term patency. The SITA grafting group received a LITA graft to the left anterior descending coronary artery plus supplemental vein or RA grafts to other coronary arteries as determined by the responsible cardiac surgeon. Surgeons could participate in ART only with prior experience of 50 or more operations using BITA grafts and were expected to be able to do either procedure in the trial.

Statistical analysis

The primary analysis used the log rank method to compare survival in the BITA and SITA groups based on the intention to treat principle and censored patients at 10 years of follow-up after the date of randomisation. Analyses to explore the influence of MAG compared with single arterial graft (SAG) included:

- per-protocol analysis comparing patients who actually received their randomly assigned treatment[16]
- as-treated analysis comparing patients who received MAG with SAG with multivariable adjustment for imbalances in baseline characteristics[16]
- impact of MAG and TAG compared with SAG[18]
- an as-treated evaluation of the impact of MAG compared with SAG based on diabetic status[19]
- exploration of interaction of age and outcome related to MAG.[20]

For the main analysis, p-values < 0.05 were considered significant for the primary outcome, and any other p-values presented were not adjusted for multiple comparisons and considered descriptive only. Other outcomes were summarised with hazard ratios (HRs) and 95% confidence intervals (CIs) and p-values where appropriate which were not used for inference of causality or to establish a relationship. Analyses were performed using Stata software, version 14 (StataCorp LP, College Station, TX, USA).[16]

For the TAG analysis, an inverse probability of treatment weighting method was used to adjust the estimate of the relative effectiveness of SAG, MAG and TAG using the as-treated approach. A propensity score model was developed adjusting for standard pretreatment covariates. We also calculated a 'TAG index' using the following formula: TAG index = number of arterial grafts/number of total grafts. This is an intuitive index of the proportion of arterial revascularisation achieved, where TAG index = 1 corresponds to TAG, whereas TAG index = 0 corresponds to revascularisation with SVG only.

Propensity score analyses were performed using R statistical software, version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria).[18]

To evaluate the effect of MAG and SAG in patients with diabetes, univariable and multivariable models were used. The multivariable model was adjusted for potential baseline confounders. In addition to the univariable and multivariable approaches, we also conducted analyses based on propensity score weighting, to ensure the robustness of our conclusion. Analyses were performed using R, version 3.2.3.[19]

To explore the interaction between age and outcome related to MAG, a Royston–Sauerbrei approach with multivariable fractional polynomials was used to model the treatment by age interaction on the all-cause mortality and the composite endpoint was used.[20] In addition, a subanalysis for the composite endpoint limited to patients between 50 and 70 years of age was performed based on clinical and statistical rationale. This age group is the most commonly represented among CABG patients and maximised the power of this subanalysis.

All analyses were performed using Stata version 14.

Results

A total of 3102 patients were enrolled (1548 BITA and 1554 SITA) between June 2004 and December 2007. 2.3% had missing vital status (dead or alive) at the final ten-year follow up and 9% had incomplete data over the course of the trial on MI, stroke and repeat revascularisation. The groups were well matched with respect to baseline covariates (see *Table 1*).[16]

Treatment

In the BITA group, 86% received BITA grafts, while in SITA, 97.5% received SITA. About 40% of procedures in both groups were performed 'off-pump' without the use of cardiopulmonary bypass and both groups received an average of three grafts. Additional RA grafts were used in 19% of patients in BITA and 22% in SITA. Medications at 10 years were well balanced between the two groups with aspirin used in 80%, beta-blockers 74%, statins 90% and angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers in 71%. *Table 2* summarises the main findings from ART.

Primary analysis at 10-year follow-up

In the BITA group 20.3% of patients had died at 10 years compared with 21.2% in SITA (HR 0.96, 95% CI 0.82 to 1.12; $p = 0.62$). The composite of all-cause mortality, MI or stroke occurred in 24.9% in BITA compared with 27.3% in SITA (HR 0.90, 95% CI 0.79 to 1.03; $p = 0.12$). There were no differences in rates of early major bleeding but there were significantly higher rates of early sternal wound complications in BITA compared with SITA [3.5% vs. 1.9% group (HR 1.81, 95% CI 1.16 to 2.81)]. Results for the primary outcome were consistent in the subgroup analyses.

The per-protocol analysis showed similar results to the intention to treat analysis. Baseline characteristics in the as-treated (non-randomised) analysis comparing MAG and SAG were similar except for a 1-year lower age in MAG. MAG was associated with reduced mortality compared with a SITA graft (adjusted HR 0.81, 95% CI 0.68 to 0.95; see *Figure 1a*) and the composite of death, myocardial or stroke (adjusted HR 0.80, 95% CI 0.69 to 0.93; see *Figure 1b*).

Effect of multiple and total arterial grafts

The final population consisted of 1084, 1010 and 390 patients in the SAG, MAG and TAG groups, respectively. The mean follow-up for this analysis was 5.2 years. Patients in the TAG group were about two years younger on average; they were less likely to present with concomitant right CAD, received fewer grafts and presented better target vessel quality and a worse New York Heart Association (NYHA) functional class but were more likely to have a left ventricular ejection fraction less than 50%. Inverse probability of treatment weighting based on propensity score created three groups comparable for all baseline characteristics.

There was a significant trend toward a reduction in 10-year mortality across the three groups (test for trend = 0.04) and TAG was associated with a reduction in all-cause death when compared with SAG (HR 0.68, 95% CI 0.48 to 0.96; $p = 0.03$) (see *Figure 2a*). The benefit of TAG was also confirmed for the composite endpoint including death, MI, stroke or repeat revascularisation (HR 0.71, 95% CI 0.53 to 0.94; $p = 0.02$) compared with SAG (see *Figure 2b*). These analyses took into consideration the potential

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TABLE 1 Demographic and clinical characteristics of the patients at baseline in the ART cohort

Characteristic, *n* (%) or *n*/*N* (%)	Bilateral-graft group (*N* = 1548)	Single-graft group (*N* = 1554)
Age at randomisation (years)	63.7 ± 8.7	63.5 ± 9.1
Male sex	1318 (85.1)	1338 (86.1)
Smoking status		
Current	237 (15.3)	214 (13.8)
Former	834 (53.9)	898 (57.8)
Never	477 (30.8)	442 (28.4)
Race		
White	1418 (91.6)	1431 (92.1)
Other	130 (8.4)	122 (7.9)
Missing data	0	1 (0.1)
Height (cm)	170.0 ± 8.5	170.4 ± 8.4
Weight (kg)	82.0 ± 13.5	81.9 ± 14.2
Body mass index	28.3 ± 4.0	28.1 ± 4.1
Blood pressure (mmHg)		
Systolic	131.7 ± 18.0	131.8 ± 18.5
Diastolic	75.0 ± 11.0	74.8 ± 11.1
Diabetes		
No history	1177 (76.0)	1191 (76.6)
Insulin-dependent	95 (6.1)	79 (5.1)
Non-insulin-dependent	276 (17.8)	284 (18.3)
Hypertension treated with drugs	1193 (77.1)	1217 (78.3)
Hyperlipidemia treated with drugs	1457/1547 (94.2)	1448/1554 (93.2)
Documented peripheral arterial disease	103 (6.7)	118 (7.6)
Documented transient ischaemic attack	53/1548 (3.4)	57/1553 (3.7)
Previous stroke	42/1548 (2.7)	48/1553 (3.1)
Previous MI	619/1547 (40.0)	681/1553 (43.9)
Previous PCI, with or without stent	242/1547 (15.6)	248/1553 (16.0)

Notes
Plus–minus values are means ± SD. Data were missing as follows: height and body mass index (the weight in kilograms divided by the square of the height in meters), for six patients in the BITA group and for two in the SITA group; weight, for two in the BITA group; and blood pressure, for three in the BITA group and one in the SITA group. Percentages may not total 100 because of rounding.
Reproduced from: Taggart DP, Benedetto U, Gerry S, Altman DG, Gray AM, Lees B, *et al*. Bilateral versus single internal-thoracic-artery grafts at 10 years. *N Engl J Med* 2019;**380**(5):437–46. https://doi.org/10.1056/NEJMoa1808783.

effect of surgeon experience by stratifying the models for the responsible surgeon who performed the operation. Intraoperative conversion from planned BITA to SITA, considered as a proxy of surgeon expertise, was associated with a higher rate of repeat revascularisation during the follow-up. The benefits of MAG and TAG were not confirmed when the analyses included only patients older than 70 years. This was consistent with another post hoc analysis investigating the interaction between age

TABLE 2 Summary of the findings from the ART main analysis and the relevant post hoc analyses

Study	Main results
ART: main analysis at 10 years	• No difference in the rate of all-cause mortality at 10-year follow-up in the intention-to-treat analysis • No difference in the rate of the composite endpoint of death, MI or stroke at 10-year follow-up in the intention-to-treat analysis
Effect of total arterial revascularisation	• Incremental benefit from single to TAG, through multiple arterial grafting, in 10-year all-cause mortality and composite endpoint of death, MI, stroke or repeat revascularisation • TAG index: the more the arterial grafts, the greater the risk reduction in 10-year mortality and composite endpoint
Interaction of diabetes and multiple arterial grafting	• In both diabetic and diabetic patients, MAG compared with SAG improves 10-year all-cause mortality and composite endpoint (death, MI or stroke) • Sternal wound infection was more frequent in the MAG group, with the highest rate in patients with insulin-dependent diabetes
Association of age with BITA outcomes	• Overall, age did not affect 10-year all-cause mortality and composite endpoint in the intention-to-treat comparison between BITA and SITA • In patients of age 50–70 years, BITA conferred a reduction in risk of composite endpoint in younger patients, suggesting that BITA could exert the largest benefit in this group

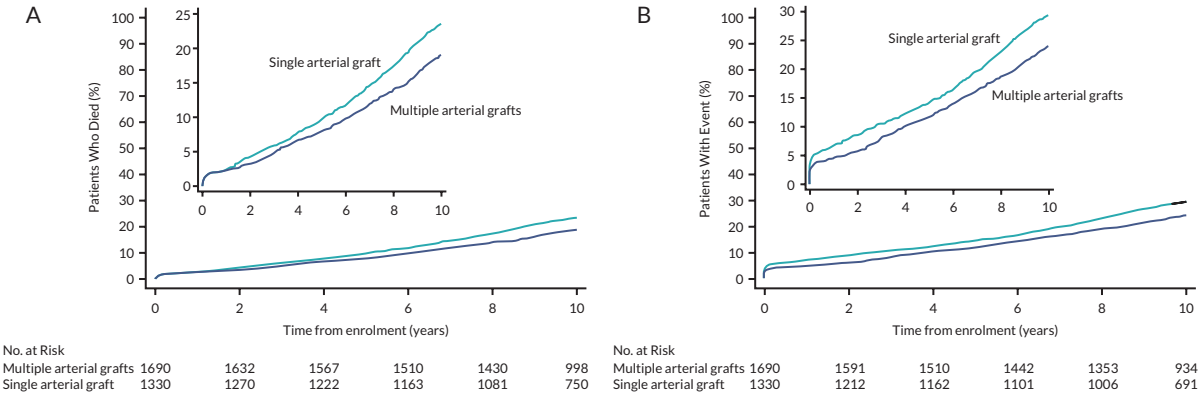


FIGURE 1 (a) As-treated analysis of MAG compared with SAG for 10-year all-cause mortality (adjusted HR 0.81; 95% CI 0.69 to 0.95). (b) As-treated analysis of MAG compared with SAG for the 10-year composite endpoint of all-cause mortality, MI or stroke (adjusted HR 0.80; 95% CI 0.68 to 0.93). Reproduced from: Taggart DP, Benedetto U, Gerry S, Altman DG, Gray AM, Lees B, *et al.* Bilateral versus single internal-thoracic-artery grafts at 10 years. *N Engl J Med* 2019;**380**(5):437–46. https://doi.org/10.1056/NEJMoa1808783.

and the 10-year outcomes following BITA compared with SITA. BITA was associated with lower rates of the composite endpoint of death, MI or stroke in patients younger than 70 years.[20]

Pooled TAG and MAG strategies showed improved 10-year mortality compared with SAG (HR 0.78, 95% CI 0.65 to 0.92; $p = 0.004$). A significant linear relationship between TAG index and the risk of 10-year mortality (HR 0.68, 95% CI 0.47 to 0.97; $p = 0.03$; see *Figure 3*) and composite outcome (HR 0.68, 95% CI 0.51 to 0.90; $p = 0.007$) was shown. Higher TAG index (> 2/3) was associated with a significantly lower risk of 10-year mortality.

Diabetes and MAG

A total of 3020 patients were included in this analysis and 24% had diabetes mellitus and about 25% of these were insulin dependent. Compared with patients without diabetes, patients with diabetes presented with a higher burden of comorbidities, including poorer left ventricular function, higher

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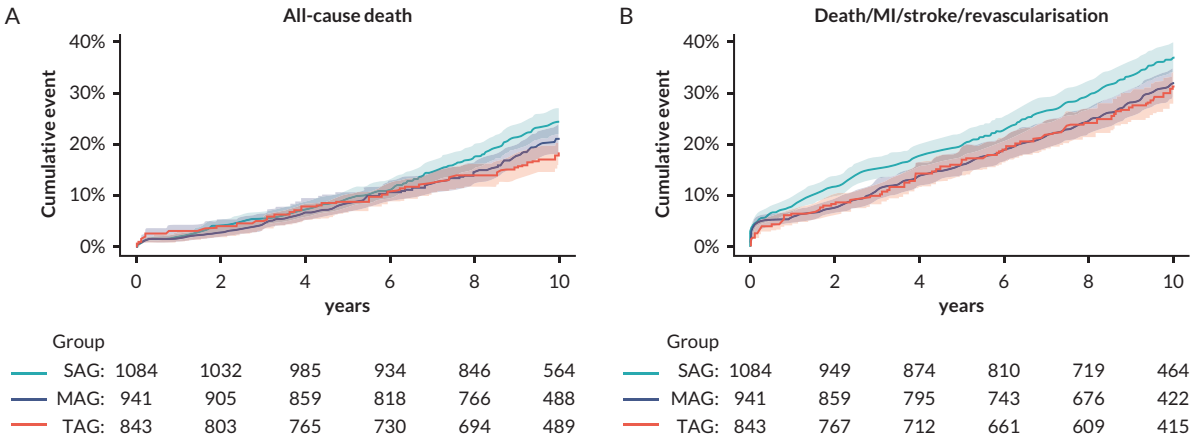


FIGURE 2 (a) Kaplan–Meier curves showing the 10-year cumulative incidence of mortality in the SAG, MAG and TAG groups. (b) Kaplan–Meier curves show the 10-year cumulative incidence of composite of death, MI, stroke or repeat revascularisation in the SAG, MAG and TAG groups. Reproduced from: Taggart DP, Gaudino MF, Gerry S, Gray A, Lees B, Dimagli A, *et al.*; ART Investigators. Effect of total arterial grafting in the Arterial Revascularization Trial. *J Thorac Cardiovasc Surg* 2022;**163**(3):1002.e–9.e6. https://doi.org/:10.1016/j.jtcvs.2020.03.013.

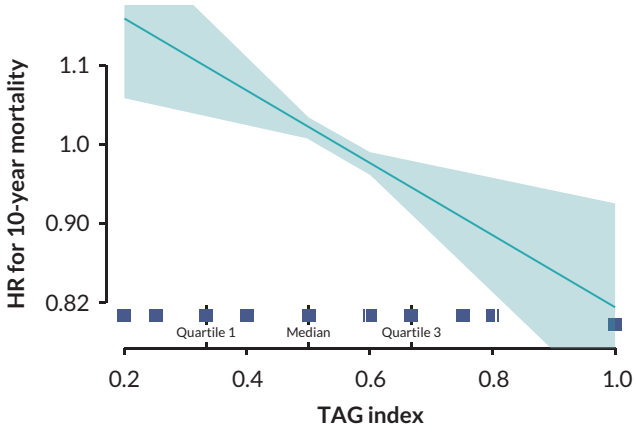


FIGURE 3 The TAG index: the ratio between the number of arterial grafts used and the number of total grafts used. The higher the index, the more arterial the surgical revascularisation. Here, the linear relationship is between the TAG index and the risk of 10-year mortality. TAG index median (0.5) as reference. Reproduced from: Taggart DP, Gaudino MF, Gerry S, Gray A, Lees B, Dimagli A, *et al.*; ART Investigators. Effect of total arterial grafting in the Arterial Revascularization Trial. *J Thorac Cardiovasc Surg* 2022;**163**(3):1002.e-9.e6. https://doi.org/10.1016/j.jtcvs.2020.03.013.

NYHA functional class and higher body mass index. According to the as-treated principle, 56% of patients in the entire cohort received MAG, and the proportion of MAG in both the diabetic and non-diabetic groups was higher than the proportion of patients receiving SAG. Baseline characteristics were comparable between the SAG and MAG groups in patients with and without diabetes.

Compared with SAG, MAG was associated with a survival benefit in both the diabetic (HR 0.68, 95% CI 0.51 to 0.91) and non-diabetic groups (HR 0.83, 95% CI 0.69 to 1.00). There was no significant treatment interaction between diabetic and non-diabetic groups, although the effect of MAG appeared greater in the diabetic group. Similarly, MAG was associated with lower rates of the composite endpoint of death, MI and stroke in the diabetic (HR 0.80, 95% CI 0.61 to 1.03) and non-diabetic groups (HR 0.78, 95% CI 0.66 to 0.93). Multivariable adjustment and propensity score weighting confirmed these results. When the analyses were restricted to comparing patients with non-insulin-dependent and insulin-independent diabetes, the results were consistent with the primary analysis. Finally, MAG was associated with higher rates of deep sternal wound infection (DSWI) compared with SAG, in both the diabetic and non-diabetic groups. Patients with insulin-dependent diabetes receiving MAG experienced

the highest absolute rate of sternal wound infection (9.6%). Use of BITA was found to be associated with the onset of sternal wound infection.

In a post hoc analysis of ART, patients receiving skeletonised LITA were found to have a higher hazard of major adverse cardiovascular outcomes (all-cause mortality, MI and revascularisation; HR 1.25, 95% CI 1.06 to 1.47).[21] Patients with skeletonised ITA experienced a higher rate of repeat revascularisation (13.5% vs. 9.9%), while the rate of sternal wound complications was higher in the pedicled group (4.5% vs. 3.3%). The findings were confirmed when only patients receiving single ITA were included in the analysis, eliminating the potential bias arising from the greater likelihood of using the skeletonisation technique with BITA.

Discussion

At 10 years, there was no apparent mortality benefit for BITA compared with SITA in the ART. Exploratory analyses suggest that there could be survival advantages for MAG by adding the RITA and/or RA graft to the LITA and this effect may be more pronounced in patients with diabetes. TAG may offer better outcomes compared with MAG or SAG. Use of BITA grafts is associated with higher rates of sternal wound complication including DSWI compared with standard LITA.

Long-term patency is the most common surrogate measure for graft efficacy after CABG, but most health systems do not routinely evaluate graft patency after CABG. Registries of patients who have undergone coronary angiography have shown greater than 90% average patency for the LITA, RITA and RA after 10 years but SVGs have average patency rates around 60%.[22–25] These registries may be prone to selection bias and, in general, patients with MAG tend to be younger with fewer comorbidities than those receiving SAG. Therefore, the estimates of arterial graft patency may be overestimated in the registries compared with the possible occurrence in unselected populations. Moreover, patency of arterial grafts can be impacted by the target vessel and surgeon experience, which may also confound observational studies. Prospective registries of unselected CABG patients to evaluate long-term graft patency are needed to understand factors associated with graft failure and computed tomography (CT) coronary angiography offers a low-risk method of doing this.

The LITA graft is generally used as a direct anastomosis to the LAD with its origin preserved, which reduces manipulation and helps to preserve graft function and integrity. Methods to harvest the LITA may influence the efficacy of the graft, with a skeletonised approach being associated with lower risk of DSWI. Traditionally, the LITA has been harvested as a pedicled graft, meaning that the accompanying tissues (veins, fascia) are dissected together with the artery. Conversely, skeletonised LITA entails dissection of the artery as an isolated conduit, free from the surrounding tissues. Studies have shown that the harvesting method of the LITA can influence sternal arterial blood supply.[26] Reduction in sternal blood supply represent an important causative element for sternal would complications. Skeletonisation allows sternal branches of the LITA to be separated as proximally as possible to the artery trunk so that the sternum can be supplied through collateral branches,[27,28] reducing the risk of sternal wound complications. However, this technique can be more challenging and technically demanding.[29,30] In addition, the need to dissect more closely to the LITA wall can increase the risk of injuries induced by electrocautery or manipulation of the vessel which can impact graft patency. The higher risk of sternal complications associated with the skeletonisation technique of harvesting ITA grafts[31,32] observed in the ART were also reported in a post hoc analysis from the Cardiovascular Outcomes for People using Anticoagulation Strategies trial.[33]

The ART has some limitations that may reduce its ability to detect potential differences between BITA and SITA grafting including a higher rate of non-compliance ('cross-over') where about 14% of patients assigned BITA actually received SITA. Another potential confounder is use of the RA graft in about 20% of patients in both BITA and SITA groups, although our exploratory analysis suggests that

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MAG is better, which should still advantage the BITA + RA group compared with LITA + RA. Ensuring greater compliance with the surgical procedures could have avoided some of the criticism of the trial although the impact of 'crossovers' on the findings in the ART are uncertain. Use of the RA may provide more advantage to the SITA group. There has also been discussion of surgeon expertise in the ART, although participating surgeons were well established in their field with documented experience of BITA grafting.[17] When ART was designed in around 2000, use of the RA and the concept of MAG during CABG was at an early stage and therefore this was not formally incorporated into the trial design.

Following our investigations on MAG, we have developed the concept of a 'TAG' index which estimates the proportion of grafts used that are arterial relative to the total number of grafts.[18] A TAG index of 1 indicates that all grafts are arterial and is generally applied when three or more grafts are used. The evidence supporting the added value of increased arterial revascularisation with three or more arterial conduits is limited. Only two randomised clinical trials compared TAG with conventional CABG. In the first trial, patients older than 70 years were randomised to either TAG or LITA plus SVG. The TAG group showed a lower rate of graft occlusion, angina recurrence, new percutaneous revascularisation and new MI, whereas the mortality at a mean follow-up of 15 months was not different.[34] The second trial was a pilot feasibility study limited to early short-term outcomes and showed that there was no difference in in-hospital mortality, stroke, DSWI and graft patency at six-month follow-up between the TAG and LITA–SVG groups.[35] Two large meta-analyses consistently concluded that TAG was associated with a survival benefit compared with MAG or SAG.[15,36]

The RA has been used as a graft for the past two decades as part of CABG. The RADIAL group has pooled data from six randomised trials with a total of 1036 patients comparing use of the RA in addition to LITA compared with SAG alone and has shown that the RA significantly reduced the rate of the composite endpoint of death, MI or repeat revascularisation (HR 0.73, 95% CI 0.61 to 0.88), the composite of death or MI (HR 0.77, 95% CI 0.63 to 0.94) and of death (HR 0.73, 95% CI 0.57 to 0.93).[37] In a meta-analysis of 12 randomised control trials, RA was identified as the best second conduit in terms of lower occlusion rate at a mean follow-up of five years.[38] There is strong and compelling evidence on the superiority of RA compared with the SVG such that the North American and European guidelines on myocardial revascularisation conferred a class I recommendation for the use of the RA for CABG.[2,3]

Individual trials of RA efficacy have been underpowered to detect changes in clinical outcomes and a meta-analysis of these trials may be subject to selection and reporting bias which can provide overestimates of efficacy. RITA and RA grafts also have subtle but possibly important structural and vasomotor differences which may affect short- and long-term patency and efficiency of blood flow. RITA shares the anatomic and biological characteristics of the LITA; RA is instead a thick vessel, with important smooth muscle component in its wall which predisposes it to a higher likelihood of spasm. As a consequence, RA could also be more sensitive to competitive flow, which can lead to graft occlusion when RA is anastomosed to a moderate-stenosed vessel (< 70%). However, a 2019 meta-analysis showed no clinical differences between RA and RITA, even though RITA was associated with higher risk of DSWI.[39]

The RITA graft can be used as an in situ graft anastomosed to the circumflex coronary artery, as a free graft separated from its origin, or as a composite 'Y' graft with the LITA. Thus, use of the RITA may also change the way in which the LITA is used possibly reducing the effectiveness of the LITA. In spite of these possibilities, registries have shown 10-year RITA patency of 90% or more.[22] On the other hand, the RA is a long conduit, which can be used as an aortocoronary graft or as a composite 'T' graft anastomosed to the LITA, and is able to form sequential anastomosis.

It is possible that the benefit from MAG does not apply homogenously to the entire CABG population, but rather represents a tailored approach for selected patients. The ART suggested an interaction effect between the treatment, age and other factors.[16] In a post hoc analysis, BITA provided a benefit in terms of composite outcome when the analysis was restricted to the younger portion of the trial cohort (50–70 years),[20] suggesting that younger patients could derive the largest benefit from BITA.

Also, in another post hoc analysis, the benefit of TAG was lost in patients older than 70 years.[18] In an analysis of 26,000 patients in the state-mandated database in New Jersey, MAG was associated with better 10-year survival but only in patients younger than 70 years.[40] This has generated the hypothesis that MAG may provide greater benefit in younger patients undergoing CABG. Similarly, patients with diabetes may benefit from MAG compared with SAG.[19,41] The main concern is related to potential higher risk of sternal wound complications when deploying the RITA as second arterial conduit. Advantages and disadvantages of MAG and TAG are summarised in *Table 3*.

There is growing evidence that MAG improves long-term outcomes, in particular survival, but this is mostly based on observational studies and a confirmatory randomised trial is needed. The use of MAG is relatively uncommon in CABG around the world (see *Figure 4*). In the 2008 *National Adult Cardiac Database Report* from the Society for Cardiothoracic Surgery in Great Britain and Ireland, the proportion

TABLE 3 The potential advantages and disadvantages of multiple and total arterial grafting

Advantages	
Multiple arterial grafting	Reduction in risk of revascularisation, MI and cardiac death from the use of RA vs. SVG
	Reduction in long-term mortality and repeat revascularisation from MAG over PCI
Total arterial grafting	Lower rate of graft occlusion, angina recurrence, new percutaneous revascularisation and new MI from TAG vs. SITA + SVG
	Benefit survival from TAG over MAG and SAG
	Reduction in risk of major adverse cardiac and cerebrovascular events, death, MI, stroke and repeat revascularisation from TAG vs. MAG
Disadvantages	
Potential increased risk of sternal wound complications with the use of BITA	
Greater technical difficulties and longer operative time with the use of BITA	
Competitive flow of grafts	

Reproduced from: Dimagli A, Benedetto U. Multiple and total arterial coronary artery bypass grafting. *AME Med J* 2020;**5**:28. https://doi.org/10.21037/amj.2020.03.12.

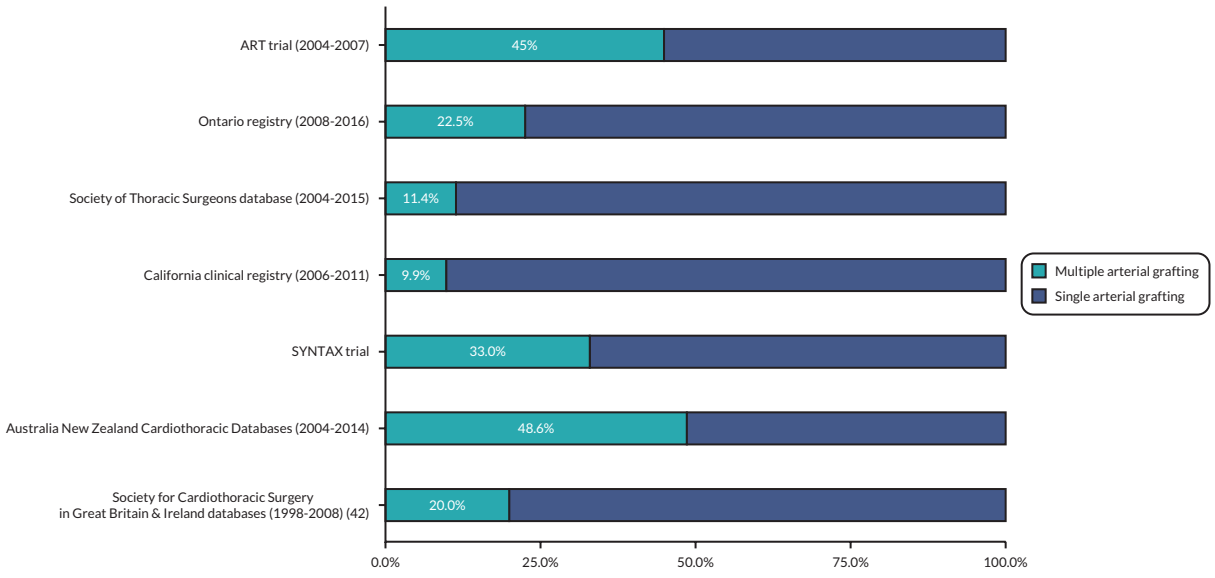


FIGURE 4 Proportion of patients receiving MAG in different databases and trials.

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of patients receiving at least two arterial grafts was as low as 20%.[42] The main two reasons that discourage surgeons from performing MAG are the lack of compelling evidence from randomised trials and the lack of confidence or expertise in performing MAG.[43]

The ART has a comprehensive health economic evaluation embedded into the protocol. The main findings were that the up-front costs of BITA are higher than SITA and these cost differences persisted at 10 years, without significant differences in quality of life years. Symptom scores are also similar at 10 years. Using the as-treated analyses MAG may be more cost-effective than SAG owing to the potential for better clinical outcomes[44,45]

Rationale and protocol outline for the Randomized Comparison of the Clinical Outcome of Single versus Multiple Arterial Grafts trial

The results of the ART have supported the Randomized Comparison of the Clinical Outcome of Single versus Multiple Arterial Grafts (ROMA) trial.[46] The hypothesis is that two or more arterial grafts compared with SAG is associated with a reduction in the primary composite endpoint of all-cause mortality, stroke, post-discharge MI or repeat revascularisation, and in the secondary endpoint of all-cause mortality. The ROMA trial is an event-driven trial enrolling at least 4300 patients younger than 70 years, with left main and/or multivessel disease undergoing primary isolated non-emergent CABG and randomised to either SAG or MAG. All patients will receive a LITA-left anterior descending anastomosis. In the SAG group, all the other stenoses will be bypassed using SVG, whereas in patients in the MAG group the main target vessel of the lateral wall will be grafted with either a RA or a RITA. The trial is powered to detect a 20% relative reduction in the primary outcome with 90% power at 5% alpha. The sample size is also sufficient to detect a 20% relative difference with 80% power at 5% alpha in overall survival.

Lessons learnt from the Arterial Revascularisation Trial

There are several lessons that can be learnt from ART as there is debate whether the results are due to a genuine lack of a treatment effect or study limitations. Issues discussed when interpreting ART include the potentially high crossover rate and use of additional arterial grafts, especially the RA in the SITA group. These factors could have impacted the power of the trial and diluted the treatment effect.[47] In the ROMA trial, a pilot phase was adopted to ensure protocol adherence and assessment of crossover. In addition, patients in the SAG group will not be allowed to receive any other arterial grafts on top of the LITA. Patients in the MAG group will be able to receive further additional arterial grafts at the judgement of the operating surgeon.

Conclusions and directions for future research

ART has shown that is possible to run pragmatic long-term trials in cardiac surgery. Overall, the study has not shown that the use of BITA is associated with reduced mortality compared with SITA. Secondary analyses from ART have generated numerous insights and hypotheses, including the potential benefit of MAG and TAG, which are being evaluated in the continuing ROMA trial. More data on long-term patency of arterial and venous grafts are needed from routine practice and we recommend that systematic prospective studies are set up using CT coronary angiography. Follow-up of ART patients to 15 years after randomisation has been supported by the British Heart Foundation and these results will be available in 2024. ART remains one of the largest and most influential trials in cardiac surgery.

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Marcus Flather (https://orcid.org/0000-0001-5644-3116) (Professor, Cardiology) drafted the report, substantially contributed to the conception of the present report, helped with acquisition and interpretation of the data, critically revised the report and provided final approval of this work.

Arnaldo Dimagli (https://orcid.org/0000-0003-0055-8656) (Research Fellow, Cardiothoracic Surgery) drafted the report, substantially contributed to the conception of the present report, helped with acquisition and interpretation of the data, critically revised the report and provided final approval of this work.

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Belinda Lees (https://orcid.org/0000-0002-8574-3967) (Clinical Trial Advisor) substantially contributed to the conception of the present report, helped with acquisition and interpretation of the data, critically revised the report and provided final approval of this work.

Alastair Gray (https://orcid.org/0000-0003-0239-7278) (Professor, Health Economics substantially contributed to the conception of the present report, helped with acquisition and interpretation of the data, critically revised the report and provided final approval of this work.

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Stephen Gerry (https://orcid.org/0000-0003-4654-7311) (Senior Medical Statistician, Statistics) substantially contributed to the conception of the present report, helped with acquisition and interpretation of the data, critically revised the report and provided final approval of this work.

Ajita Naik (https://orcid.org/0000-0001-7398-4643) (Research Fellow, Cardiothoracic Surgery) substantially contributed to the conception of the present report, helped with acquisition and interpretation of the data, critically revised the report and provided final approval of this work.

Jo Cook (https://orcid.org/0000-0001-6821-5030) (Senior Clinical Trial Manager) substantially contributed to the conception of the present report, helped with acquisition and interpretation of the data, critically revised the report and provided final approval of this work.

Mario Gaudino (https://orcid.org/0000-0003-4680-0815) (Professor, Cardiothoracic Surgery) substantially contributed to the conception of the present report, helped with acquisition and interpretation of the data, critically revised the report and provided final approval of this work.

Matthew Little (https://orcid.org/0000-0002-2680-5697) (Consultant, Health Economics) substantially contributed to the conception of the present report, helped with acquisition and interpretation of the data, critically revised the report and provided final approval of this work.

David P Taggart (https://orcid.org/0000-0001-5343-5997) (Professor, Cardiothoracic Surgery) substantially contributed to the conception of the present report, helped with acquisition and interpretation of the data, critically revised the report and provided final approval of this work.

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

This report is dedicated to the memory of Professor Doug Altman, who was a founding member of the ART team and died on 3 June 2018.

Data-sharing statement

The data underlying this article will be shared on reasonable request to the corresponding author.

List of publications from the Arterial Revascularisation Trial

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Appendix 1 Centres participating in the Arterial Revascularisation Trial

Principal investigators (shown in bold), co-investigators and coordinators (number of patients enrolled).

1. John Radcliffe Hospital, Oxford, UK. **D Taggart**, Ratnatunga, S Westaby, J Cook, C Wallis (427)
2. Medical University of Silesia (2nd Department of Cardiac Surgery), Katowice, Poland. **S Wos, M Jasinski, M Deja**, K Widenka, A Blach, R Gocol, D Hudziak, P Zurek, R Bachowski, R Mrozek, T Kargul, W Domarardzki, J Frackiewicz (256)
3. Edinburgh Royal Infirmary, Edinburgh, UK. **V Zamvar**, D Ezakadan (217)
4. Austin and Repatriation Medical Centre, Melbourne, Australia. **B Buxton, S Seevanayagam**, G Matalanis, A Rosalion, J Negri, S Moten, V Atkinson, A Newcomb, P Polidano, R Pana, S Gerbo (192)
5. University Hospital of Wales, Cardiff, UK. **P O'Keefe**, U von Oppell, D Mehta, A Azzu, A Szafranek, E Kulatilake, J Evans, N Martin, D Banner (185)
6. Royal Sussex County, Brighton, UK. The late **A Forsyth, U Trivedi,** J Hyde, A Cohen, M Lewis, E Gardner, A MacKenzie, N Cooter, E Joyce, J Parker, F Champney (180)
7. Freeman Hospital, Newcastle, UK. **S Clark**, J Dark, K Tocewicz, T Pillay, S Rowling, J Adams-Hall (152)
8. Medical University of Silesia (1st Department of Cardiac Surgery), Katowice, Poland. **A Bochenek, M Deja**, M Cisowski, M Bolkowski, W Morawski, M Guc, M Krejca, M Wilczynski, A Duralek, W Gerber, J Skarysz, R Shrestha, W Swiech, P Szmagala, L Krzych, A Pawlak, K Kepa (145)
9. Royal Infirmary, Manchester, UK. **R Hasan**, D Keenan, B Prendergast, N Odom, K McLaugh-lin, G Cummings-Fosong, C Mathew, H Iles-Smith, A Oomen (115)
10. King's College Hospital, London, UK. **J Desai**, A El-Gamel, L John, O Wendler, M Andrews, K Rance, R Williams, V Hogervorst, J Gregory, J Jessup, A Knighton, A Hoare (114)
11. Royal Papworth Hospital, Cambridge, UK. **A Ritchie, C Choong, S Nair, C Sudarshan**, D Jenkins, S Large, M Barman, K Dhital, T Routledge, B Rosengard, H Munday, K Rintoul, E Jarrett, S Lao-Sirieix, A Wilkinson, L Garner, J Osmond, H Holcombe (101)
12. Castle Hill Hospital, Hull, UK. **A Cale**, S Griffin, J Dickson, J Cook (97)
13. Glenfield Hospital, Leicester, UK. **T Spyt, A Gershlick**, M Hickey, A Sosnowski, G Peek, J Szostek, L Hadjinikalaou, E Logtens, M Oakley, S Leji (95)
14. Harefield Hospital, London, UK. **J Gaer**, M Amrani, G Dreyfus, T Bahrami, F de Robertis, K Baig, G Asimakopoulos, H Vohra, V Pai, S Tadjkarimi, Soleimani, G Stavri, G Bull, H Collappen (94)
15. John Paul II, Krakow, Poland. **J Sadowksi, B Kapelak**, B Gaweda, P Rudzinski, J Stolinski, J Konstanty-Kalandyk, (92)
16. Heart Institute of Pernambuco, Recife, Brazil. **F Moraes**, C Moraes, J Wanderley (82)
17. Royal Brompton Hospital, London, UK. **J Pepper**, A De Souza, M Petrou, R Trimlett, T Morgan, J Gavino, SF Wang (82)
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