1-year costs of Bilateral or Single Internal Mammary Grafts in the Arterial Revascularisation Trial

Short title: 1-year costs of Bilateral or Single Internal Mammary Grafts

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Abstract

Objective: Coronary artery bypass grafting (CABG) using bilateral internal mammary arteries (BIMA) may improve survival over CABG using single internal mammary arteries (SIMA), but may be surgically more complex (and therefore costly) and associated with impaired sternal wound healing. We report, for the first time, a detailed comparison of health care resource use and costs over 12 months, as part of the Arterial Revascularisation (ART) Trial.

Methods: 3102 patients in 28 hospitals in 7 countries were randomised to CABG surgery using BIMA (n=1548) or SIMA (n=1554). Detailed resource use data were collected covering surgery, the initial hospital episode, and for 12 months post randomisation. Using UK unit costs, total costs were calculated and compared between trial arms and for sub-groups.

Results: Patients randomised to BIMA spent 20 minutes longer in theatre (95% CI 15 to 25, p<0.001), and also required more treatment for sternal wound problems. Mean (SD) total costs per patient at 12 months were £13,839 (£10,534) for BIMA and £12,717 (£9,719) for SIMA (mean cost difference £1122, 95% CI £407 to £1,838, p=0.002). No tests for interaction between subgroups and treatment allocation were significant.

Conclusions: At 12 months from randomisation, mean costs were approximately 9% higher in BIMA than SIMA patients, primarily due to longer time in theatre and in-hospital stay, and slightly higher costs related to sternal wound problems during follow-up. Follow-up to the primary trial endpoint of 10 years will reveal whether longer-term differences emerge in graft patency or in overall survival.

KEY MESSAGES

What is already known about this subject?

Coronary artery bypass grafting is a safe, effective and high volume procedure, but patient outcomes might be further improved by using bilateral internal mammary arteries (BIMA), which may offer better long-term graft patency and survival. No randomised comparison of the costs of these procedures has been published.

What does this study add?

Using data from the Arterial Revascularisation Trial, we show that at 12 months from randomisation costs were approximately 9% higher in BIMA than SIMA patients, mainly due to longer time in theatre and in-hospital stay, and slightly higher costs related to sternal wound problems during follow-up. These cost differences were larger in some sub-groups, such as diabetes vs. non-diabetes.

How might this impact on clinical practice?

Our findings will be valuable to clinicians and health policy makers considering the potential cost implications of moving from SIMA to BIMA, for all eligible patients or particular sub-groups. Researchers will require these cost estimates to assess the long-term cost-effectiveness of BIMA.

KEYWORDS

Revascularization; Bypass; Costs

INTRODUCTION

During coronary artery bypass grafting (CABG) most patients receive three bypass grafts, one to each of the major coronary arteries. For almost three decades routine practice has been to graft a single internal mammary artery (SIMA) to the left anterior descending coronary artery and to use vein or radial artery grafts to the other coronary arteries.(1) Better long-term patency of mammary artery grafts and evidence of improved 10-year survival and reductions in recurrent angina, myocardial infarction and repeat revascularisation suggest that patient outcomes could be further improved by using bilateral internal mammary arteries (BIMA).(2) However, concerns that BIMA is technically more challenging and may increase surgery-related mortality and sternal wound complications have restrained use of BIMA in Europe or the USA: it accounted for fewer than 5% of US cases in 2009.(3-5)

A meta-analysis reported a significant reduction in mortality with BIMA over SIMA (hazard ratio 0.79; 95% CI 0.75 to 0.84) across nine observational studies including 15,583 patients with mean follow-up exceeding nine years.(6) However evidence from randomised trials of long-term survival benefits with BIMA is still awaited. The multinational Arterial Revascularisation Trial (ART) (one of the largest trials ever conducted in cardiac surgery) randomised 3102 CABG patients to SIMA (n=1554) or BIMA (n=1548) and will eventually provide valuable information on the impact of BIMA on 10-year survival and the need for repeat revascularisation.(7) ART has however already reported on the 'safety' of the procedure, finding similar clinical outcomes across trial arms at one-year post randomisation, and a small absolute increase (1.3%) in the need for sternal wound reconstruction with BIMA.(8)

As CABG is a high volume procedure (in England and Wales, for example, around 16,000 first time surgeries annually) it is important to consider the potential impact on costs as well as effectiveness of a move from SIMA to BIMA grafts. Therefore a health economic evaluation was designed as an integral part of ART and will ultimately report on the cost-effectiveness of BIMA versus SIMA at 10 years. Here we report an analysis of detailed health care resource use data collected in each trial arm out to one-year post randomisation, allowing unbiased comparison of the costs of SIMA and BIMA for the first time, and direct quantification of any short-term cost increases with BIMA on account of additional surgical complexities and impaired wound healing. Secondary aims are to explore resource use and cost differences between SIMA and BIMA for clinical subgroups where surgical outcomes could differ, and to consider variations in resource use across different countries in the trial.

The findings should be of interest to clinicians and health policy makers considering the potential cost implications of moving from SIMA to BIMA, and will also be essential inputs into the final cost-effectiveness analysis of the ART trial, alongside estimates of longer-term costs, repeat revascularisation, survival, and health related quality of life.

METHODS

Full details of the ART protocol, baseline and one year safety outcomes are published elsewhere.(7, 8) ART is a multi-centre randomised controlled trial involving 28 hospitals across seven countries and randomised CABG patients in a 1:1 ratio to receive SIMA or BIMA grafts. Patients were eligible for ART if they had multi-vessel coronary artery disease and were to undergo CABG. Patients requiring

single grafts or re-do CABG were excluded. The ART study complied with the Declaration of Helsinki. Prior ethical approval was obtained in participating centres and each patient was required to provide written informed consent. The Clinical Trials and Evaluation Unit (CTEU) at the Royal Brompton and Harefield NHS Foundation Trust in London provided central co-ordination, and the study was sponsored by the University of Oxford.

ART was designed to detect an absolute 5% reduction in 10-year all-cause mortality (from 25% to 20%) with 90% power at a 5% significance level, and randomised 1554 patients to SIMA and 1548 patients to BIMA between 30th June 2004 and 20th December 2007. Data on health care resource use and health-related quality of life (EuroQol EQ-5D and shortened World Health Organisation Rose Angina Questionnaire)(9, 10) are also being collected.

Measurement of resource use

During the initial inpatient admission data were collected for each patient on time in theatre (arrival in the anaesthetic room to final skin closure), total cardiopulmonary bypass time, blood products, platelets and fresh frozen plasma used, use of a cell saver machine for autologous blood transfusion, occurrence and duration of return to theatre, need for additional PRBCs, time receiving ventilation, use of an intra-aortic balloon pump, days receiving inotropic support or renal support therapy, and use of haemofiltration drugs.

Patient level data were also collected on treatments for sternal wound infections (antibiotics, debridement, vacuum assisted closure (VAC) dressings, and / or sternal reconstruction), serious adverse events (myocardial infarction, cerebrovascular accident, major bleed/other vascular events, further CABG or

PTCA, and other), total hours in intensive care (ITU), total days in high dependency units (HDU), and total days on a cardiac surgery ward.

Discharge to home, local hospital, nursing home, or elsewhere was recorded, as were medications prescribed. At six weeks post randomisation information was collected on medication use, subsequent sternal wound infections and their treatment, serious adverse events, visits to a General Practitioner (GP), practice nurse, hospital outpatient clinic, or cardiac rehabilitation clinic, and duration of any hospital readmission. These same data were captured by telephone interview at 12 months post randomisation.

Measurement of Costs

Costs were not evaluated separately for each geographical location (by centre or country). Instead, UK unit costs (£ 2013/14) taken from national and local sources were used to value all patient-level resource use data. The perspective used was that of the healthcare system, and out-of-pocket costs such as travel to GP surgeries were not collected. Hospital costs are based on standard tariffs such as NHS reference costs. Where individual drug usage was not available, for example for antibiotics after surgery, assumptions based on clinical opinion and local procedures at one UK hospital were used. Supplementary Table 1 and accompanying text provide a detailed description of sources, methods and assumptions.

Statistical Analysis

Approximately 4% of trial resource use data items were missing across the 12 months; these were assumed to be missing at random and multiple imputation (MI) with chained individual linear or logistic regression equations was used to impute

missing values for each variable.(11) All imputation equations included age, gender, treatment allocation, diabetes, and smoking. Five values were imputed for each missing data cell and Rubin's Rule used to summarise across the imputed datasets.(11)

Continuous data were summarised using means and standard deviations and categorical data using percentages. When comparing between trial arms, mean differences and 95% confidence intervals for differences were calculated, and two-sample t-tests were applied. All data analyses were performed using STATA 12 (StataCorp, College Station, Texas).

Sensitivity Analyses

The low frequency of many events (for example inpatient SAEs and sternal wound reconstructions) and the low unit costs of many elements of care (for example inhalational anaesthetics) mean that even extreme changes to many unit costs and resource use assumptions would not significantly change study results. Sensitivity analyses were used to explore the effect of imputing missing data, and of including only patients who received the surgery they were allocated.

Sub-group Analyses

Resource use and costs were compared between BIMA and SIMA arms for the following sub-groups: diabetic vs non-diabetic, age ≥ 70 years vs <70 years, on-pump vs off-pump, prior vs no prior MI, New York Heart Association (NYHA) Class I and II vs NYHA Class III and IV, and Canadian Cardiovascular Society (CCS) class 0, I and II vs CCS class III and IV. 12-month costs were also compared across the

three countries each recruiting more than 100 patients to the trial (UK, Poland, Australia).

RESULTS

Table 1 shows the baseline characteristics for patients in each arm of the trial. The groups were well balanced with respect to demographic and clinical characteristics, and disease/symptom severity.

Table 1: Baseline demographic and clinical characteristics by trial arm

	SIMA (n=1554)	**BIMA (n=1548)**
Male – n (%)	1338 (86.1)	1318 (85.1)
Age at randomisation– mean (SD)	63.5 (9.1)	63.7 (8.7)
Country – n (%)		
UK	1021 (65.7)	1032 (66.4)
Poland	311 (20.0)	295 (19.0)
Australia	95 (6.1)	97 (6.2)
India	48 (3.1)	40 (2.6)
Brazil	40 (2.6)	42 (2.7)
Italy	27 (1.7)	34 (2.2)
Austria	12 (1.0)	8 (1.0)
Body mass index – mean (SD)	28.1 (4.1)*	28.3 (4.0)†
Systolic blood pressure (mmHg) – mean (SD)	131.8 (18.5)‡	131.7 (18.0)§
Diastolic blood pressure (mmHg) – mean (SD)	74.8 (11.1)‡	75.0 (11.0)§
Diabetic – n (%)	363 (25.3)	371 (24.0)
Prior myocardial infarction – n (%)	681 (43.8)‡	619 (40.0)‡
NYHA class – n (%)*		
I	481 (31.0)	481 (31.1)
II	747 (48.1)	722 (46.6)
III	263 (16.9)	279 (18.0)
IV	61 (3.9)	66 (4.3)
CCS class – n (%)		
No angina	128 (8.2)	132 (8.5)
I	355 (22.8)	348 (22.5)
II	598 (38.5)	582 (37.6)
III	351 (22.6)	368 (23.8)

IV	122 (7.9)	118 (7.6)
Received Surgery – n (%)	1546 (99.5)	1531 (98.9)

*Missing for 2 patients, †Missing for 6 patients, ‡Missing for 1 patient, §Missing for 3 patients

Sternal wound infections were infrequent but twice as many occurred in patients in the BIMA arm than in the SIMA arm (3.3% v 1.6% respectively). Sternal wound infection occurring in combination with dehiscence also affected more patients in the BIMA arm (1.6% v 0.6% respectively). Mortality at 30 days and 12 months was similar across both trial arms.

Table 2 shows mean resource use and costs per patient for the initial inpatient admission by trial arm (intention to treat) for all patients. The cost of initial surgery, cost of initial inpatient admission (not including initial surgery), and the cost between discharge and 12 month follow-up are also shown in Figure 1 for each trial arm. Theatre duration in the BIMA arm was on average 20 minutes longer than in the SIMA arm (95% CI 15 to 25, $p<0.002$). There were no statistically significant differences between trial arms in time on cardiopulmonary bypass, blood product utilisation or use of cell saver equipment, and similar proportions of patients in both arms were returned to theatre. In the immediate post-operative period, time on ventilation and usage of intra-aortic balloon pumps, inotropes, renal support therapy, and haemofiltration were similar between arms.

The proportion of patients receiving treatments for sternal wound problems was small, but significantly more patients in the BIMA arm had treatment involving antibiotics, VAC dressings, and underwent debridement and sternal wound reconstruction (Table 2). The proportion of patients experiencing serious events during the initial inpatient episode was similar in both arms, but with a trend towards an increased number of subsequent revascularisations with PTCA in the BIMA arm.

On average patients in the BIMA arm spent an additional two hours in ITU and stayed a third of a day longer on cardiac surgery wards (Table 2).

Table 2: Mean resource use and cost (UK £ 2013-14) per patient by trial arm for the initial inpatient admission

Resource use/cost category	Mean resource use (SD) or n (%) of patients receiving resource		Mean difference in resource use (95% CI, p-value)	Mean cost (SD)		Mean difference in costs (95% CI, p-value)
	SIMA (n=1554)	**BIMA (n=1548)**	**BIMA vs. SIMA**	**SIMA (n=1554)**	**BIMA (n=1548)**	**BIMA vs. SIMA**
Initial Surgery						
Time in theatre (minutes)	254 (72)	274 (74)	20 (15, 25; 0.000)	-	-	-
Duration related theatre costs and staff	-	-	-	5016 (1416)	5414 (1473)	399 (297, 501; 0.000)
Duration related anaesthetic costs	-	-	-	10 (1)	10 (1)	0 (0, 0; 0.610)
Time on bypass (minutes)	52 (50)	50 (50)	-2 (-6, 1; 0.183)	13 (12)	12 (12)	-1 (-2, 0; 0.135)
Surgery related consumables, n (%)	1532 (99)	1505 (98)	-1.1 (-2.1, 0.1; 0.027)	454 (73)	447 (87)	-7 (-12, -1; 0.018)
Aprotinin during surgery, n (%)	372 (24)	368 (24)	-0.1 (-3.2, 2.9; 0.921)	77 (137)	76 (136)	0 (-10, 9; 0.921)
Red blood cells transfused (ml)	67.9 (228.0)	66.9 (334.1)	-1.0 (-21.3, 19.2; 0.920)	36 (114)	35 (154)	-1 (-10, 9; 0.918)
Platelets (ml)	9.4 (73.1)	10.6 (68.2)	1.2 (-3.9, 6.2; 0.646)	9 (69)	11 (67)	1 (-4, 6; 0.627)
Fresh Frozen Plasma (ml)	20.8 (120.0)	26.4 (147.1)	5.6 (-4.2, 15.4; 0.262)	3 (17)	4 (21)	1 (-1, 2; 0.282)
Use of cell saver, n (%)	490 (31.5)	474 (30.6)	-0.9 (-4.2, 2.5; 0.602)	32 (47)	31 (47)	-1 (-4, 2; 0.597)
Aprotinin following surgery, n (%)	89 (5.7)	98 (6.3)	0.6 (-1.1, 2.3; 0.471)	18 (74)	20 (78)	2 (-3, 7; 0.471)
Total initial surgery costs	-	-		**5668 (1508)**	**6062 (1618)**	**393 (283, 504; 0.000)**
Returned to theatre						
Patients returning to theatre, n (%)	54 (3.5)	66 (4.3)	0.8 (-0.6 , 2.1; 0.255)	106 (762)	109 (564)	3 (-44, 50; 0.900)
Immediate post-operative period						
Ventilation time (minutes)	858 (3279)	963 (3051)	105 (-120, 330; 0.359)	519 (1984)	583 (1846)	64 (-72, 200; 0.359)
Intra-aortic balloon pump, n (%)	57 (3.7)	68 (4.4)	0.7 (-0.7, 2.1; 0.305)	21 (105)	25 (115)	4 (-4, 12; 0.305)
Inotropic support (days)	0.7 (2.9)	0.7 (1.4)	-0.02 (-0.2, 0.1; 0.768)	4 (17)	4 (10)	0 (-1, 1; 0.676)
Renal support therapy (days)	0.1 (0.9)	0.2 (2.2)	0.1 (-0.03, 0.2; 0.126)	86 (590)	148 (1501)	63 (-18, 143; 0.126)
Hemofiltration, n (%)	207 (13.3)	222 (14.4)	1.0 (-1.4, 3.4; 0.419)	0.1 (0.4)	0.1 (0.5)	0 (0, 0; 0.335)
In-hospital sternal wound problems*, n (%)						
Treatment including antibiotics,	8 (0.5)	22 (1.4)	0.9 (0.2,1.6; 0.010)	0 (5)	1 (16)	1 (0, 2; 0.002)
Treatment including debridement,	2 (0.1)	11 (0.7)	0.6 (0.1, 1.0; 0.012)	3 (86)	22 (309)	19 (3, 34; 0.023)
Treatment including vac dressing,	2 (0.1)	9 (0.6)	0.5 (0.1, 0.9; 0.034)	0 (10)	2 (30)	2 (0, 3; 0.038)
Treatment including reconstruction,	2 (0.1)	13 (0.8)	0.7 (0.2, 1.2; 0.004)	6 (171)	40 (434)	34 (11, 57; 0.004)
Total cost of sternal wound problems	-	-	-	**10 (266)**	**65 (714)**	**55 (17, 93; 0.004)**

In-hospital SAE treatment, n (%)						
Myocardial Infarction	25 (1.6)	26 (1.7)	0.1 (-0.8, 1.0; 0.877)	15 (116)	15 (119)	1 (-8, 9; 0.877)
Cerebrovascular accident	17 (1.1)	15 (1.0)	-0.1 (-0.8, 0.6; 0.731)	12 (114)	11 (118)	-1 (-9, 7; 0.874)
Further CABG	2 (0.1)	5 (0.3)	0.2 (-0.1, 0.5, 0.254)	6 (177)	16 (280)	10 (-7, 26; 0.254)
Further PTCA	1 (0.1)	8 (0.5)	0.5 (0.1, 0.8; 0.019)	1 (59)	15 (229)	14 (2, 26; 0.020)
Revascularisation with catheter	3 (0.2)	1 (0.1)	-0.1 (-0.4, 0.1; 0.319)	3 (72)	1 (42)	-2 (-6, 2; 0.319)
Major bleed	36 (2.3)	42 (2.7)	0.4 (-0.7, 1.5; 0.481)	132 (877)	169 (1052)	36 (-32, 105; 0.296)
In-hospital stay						
Time in ITU (hours)	35.3 (102.7)	37.7 (90.6)	2.4 (-4.5, 9.2; 0.497)	946 (2751)	1009 (2428)	63 (-119, 246; 0.497)
Time in HDU (days)	1.2 (3.0)	1.3 (3.2)	0.1 (-0.2, 0.3; 0.732)	450 (1121)	464 (1186)	14 (-67, 95; 0.732)
Time on general cardiac wards (days)	6.9 (5.6)	7.2 (6.5)	0.3 (-0.2, 0.7; 0.201)	1831 (1481)	1905 (1721)	74 (-39, 187; 0.201)
Total cost, initial inpatient admission	-	-	-	**9811 (6390)**	**10601 (6601)**	**791 (333, 1248; 0.001)**

* Categories are not mutually exclusive (for example a patient receiving antibiotics and a vac dressing would appear under both headings).

The total cost of the initial inpatient admission was £10,601 (£6,601) in the BIMA arm and £9,811 (£6,390) in the SIMA arm, giving a mean cost increase of £791 per patient (95% CI £333 to £1,248, p<0.001). Results were similar after adjustment for age, sex and diabetes: BIMA was associated with a cost increase of £778 (95% CI £323 to £1233, p=0.001) over the initial inpatient admission. Longer time in theatre and on various hospital wards by patients in the BIMA arm accounted for approximately two thirds of additional costs incurred. Treatments for additional sternal wound problems accounted for a further 7%, and renal support therapy and longer ventilation time for a further 8% each.

Table 3 shows mean resource use and cost per patient in each trial arm from initial hospital discharge to 12 months follow-up. Similar proportions of patients in each arm were transferred to local hospitals, nursing homes and other institutions. At six weeks the overall number of patients requiring treatment for sternal wound problems was small but more patients in the BIMA arm received antibiotics and debridement.

The two trial arms were comparable in terms of GP and nurse visits, cardiac rehabilitation visits and hospital readmissions to 12 months, but patients in the BIMA arm had on average 0.5 more (95% CI 0.1 to 0.9, p=0.015) hospital outpatient clinic visits than patients in the SIMA arm. There were no differences between trial arms in the proportion of participants experiencing serious adverse events, or the cost of these, between discharge and 12 months.

The total cost of the follow-up period from hospital discharge was £3,238 (£7,118) in the BIMA arm and £2,906 (£6,203) in the SIMA arm (mean cost difference £332, 95% CI -£141 to £805, p=0.169). The mean overall total cost per patient out to 12 months from randomisation was £13,839 (£10,534) in the BIMA arm

and £12,717 (£9,717) in the SIMA arm (mean cost difference £1122, 95% CI £407 to £1,838, p=0.002) (Figure 1).

Figure 1: Mean (95% CI) per-patient cost by trial arm at various follow-up time points

(*see separate file)

Table 3: Mean resource use and cost (UK £ 2013-14) per patient by trial arm from hospital discharge to 12-month follow-up

e	Mean resource use (SD) or n (%) of patients receiving resource		Mean difference in resource use (95% CI, p-value)	Mean cost (SD)		Mean difference in costs (95% CI, p-value)
	SIMA (n=1554)	**BIMA (n=1548)**	**BIMA vs. SIMA**	**SIMA (n=1554)**	**BIMA (n=1548)**	**BIMA vs. SIMA**
At hospital discharge, n (%)						
Home	1320 (85.0)	1311 (84.7)	-0.2 (-2.8, 2.3; 0.853)	-	-	-
Transferred to local hospital	157 (10.1)	158 (10.2)	0.1 (-2.0, 2.2; 0.915)	189 (563)	198 (588)	10 (-31, 50; 0.644)
Transferred to nursing home	6 (0.4)	5 (0.3)	-0.1 (-0.5, 0.4; 0.768)	221 (3558)	185 (3255)	-36 (-276, 204; 0.768)
Transferred to other institution	56 (3.6)	56 (3.6)	-0.0 (-1.3, 1.3; 0.986)	101 (524)	101 (523)	0 (-37, 37; 0.986)
Referral for cardiac rehabilitation	1208 (77.7)	1228 (79.3)	1.6 (-1.3, 4.5; 0.273)	-	-	-
Sternal wound problems to 6 weeks*, n (%)						
Treatment with antibiotics	16 (1.0)	30 (1.9)	0.9 (0.1, 1.7; 0.036)	1 (12)	2 (14)	0 (0, 1; 0.294)
Treatment with debridement	10 (0.6)	22 (1.4)	0.8 (0.1, 1.5; 0.032)	15 (191)	35 (301)	20 (2, 38; 0.026)
Treatment with vac dressing	10 (0.6)	17 (1.1)	0.4 (-0.2, 1.1; 0.173)	2 (23)	3 (30)	1 (-1, 3; 0.173)
Treatment with reconstruction	4 (0.3)	11 (0.7)	0.4 (-0.1, 0.9; 0.069)	12 (241)	34 (400)	22 (-2, 45; 0.069)
Total cost of sternal wound problems	-	-	-	**103 (1045)**	**246 (1976)**	**143 (32, 254; 0.012)**
Mean number of medications (SD)	3.3 (1.1)	3.3 (1.1)	0.0 (-0.1, 0.1; 0.960)	56 (73)	59 (73)	3 (-3, 8; 0.372)
Health care contacts discharge to 12 months						
GP visits	6.5 (5.0)	6.3 (5.2)	-0.2 (-0.5, 0.2; 0.328)	298 (231)	290 (240)	-8 (-25, 8; 0.328)
Nurse visits	3.1 (8.2)	3.4 (8.2)	0.3 (-0.3, 0.8; 0.357)	43 (112)	47 (112)	4 (-4, 12; 0.357)
Outpatient clinic visits	1.9 (2.2)	2.4 (7.5)	0.5 (0.1, 0.9; 0.015)	252 (293)	316 (987)	64 (13,115; 0.015)
Cardiac rehabilitation visits	5.1 (8.9)	5.2 (8.7)	0.1 (-0.5, 0.7; 0.717)	383 (541)	391 (532)	8 (-30, 47; 0.667)
Hospital admissions	0.3 (0.8)	0.3 (0.8)	0.0 (-0.1, 0.1; 0.594)	-	-	-
Number of nights in hospital	2.6 (8.9)	3.1 (11.5)	0.5 (-0.3, 1.2; 0.208)	685 (2356)	812 (3038)	127 (-71, 325; 0.208)
SAE treatment from discharge to 12 months, n (%)						
Myocardial Infarction	10 (0.6)	9 (0.6)	-0.1 (-0.6, 0.5; 0.825)	13 (171)	11 (152)	-3 (-14, 9; 0.665)
Cerebrovascular accident	13 (0.8)	8 (0.5)	-0.3 (-0.9, 0.3; 0.278)	22 (267)	12 (190)	-11 (-27, 6; 0.200)
Further CABG	-	1 (0.1)	0.1 (-0.1, 0.2; 0.316)	-	5 (206)	5 (-5, 15; 0.316)
Further PTCA	22 (1.4)	19 (1.2)	-0.2 (-1.0, 0.6; 0.646)	53 (463)	41 (392)	-11 (-41, 19; 0.469)
Revascularisation with catheter	3 (0.2)	8 (0.5)	0.3 (-0.1, 0.7; 0.129)	4 (97)	15 (223)	11 (-1, 24; 0.063)

Major bleed	5 (0.3)	6 (0.4)	0.1 (-0.3, 0.5; 0.758)	27 (487)	36 (643)	8 (-32, 48; 0.686)
Other AEs (cost of hospital stay only)	276 (17.8)	254 (16.4)	-1.3 (-4.0, 1.3; 0.317)	405 (2219)	450 (2752)	45 (-131, 221; 0.614)
Death (cost of hospital stay only)	21 (1.3)	20 (1.3)	-0.1 (-0.9, 0.7; 0.885)	51 (999)	23 (647)	-28 (-87, 31; 0.357)
Total costs from discharge to 12 months	**-**	**-**	**-**	**2906 (6203)**	**3238 (7118)**	**332 (-141, 805; 0.169)**
Total overall costs at 12 months	**-**	**-**	**-**	**12717 (9719)**	**13839 (10534)**	**1122 (407, 1838; 0.002)**

*categories are not mutually exclusive (for example a patient receiving antibiotics and a vac dressing would appear under both headings)

Results were similar after adjustment for age, sex and diabetes: BIMA was associated with £1081 (95% CI £376 to £1787, p=0.003) higher costs per patient out to 12 months from randomisation.

Sensitivity Analysis

1494 of the 1554 patients allocated to SIMA and 1294 of the 1548 patients allocated to BIMA received the allocated procedure. Supplementary Table 2 reports a "per protocol" analysis comparing costs by trial arm: as in the base case analysis, total inpatient costs were significantly greater for those receiving BIMA than for SIMA, and total costs at 12 months were significantly greater for BIMA than for SIMA (£1,243 more costly for BIMA, with 95% CI £501 to £1,985, p<0.001).

Supplementary Table 3 reports total costs by trial arm when no multiple imputation was performed and calculations were based on "complete cases" only. As in the base case analysis, the total cost of the initial hospital stay was significantly greater for BIMA than for SIMA, driven by time in theatre and ward stays, and there was a non-significant trend towards BIMA being more costly than SIMA at 12 month follow-up.

Sub-group Analyses

Table 4 shows total costs to 12 months for the various sub-group analyses and country comparisons; Supplementary Tables 4-10 provide full details. Tests showed no evidence of interaction between subgroup and treatment allocation, although additional costs with BIMA for diabetic patients were more than twice those of non-diabetic patients (£2,119 v £803 per patient respectively), for on-pump patients were

more than twice those for off-pump patients (£1,575 v £623 per patient respectively), and also were higher for patients with more severe angina and cardiac disease.

Table 4: Total costs to 12-months follow-up by trial arm and by various subgroups

Subgroup	Mean total cost (SD)		Mean difference in total cost (95% CI, p-value)*
	SIMA	BIMA	BIMA vs. SIMA
No history of diabetes (n=2368)	12555 (9617)	13557 (9788)	803 (18 , 1587 ; 0.045)
Insulin/non-insulin dependent diabetes (n=734)	13249 (10042)	15369 (12504)	2119 (473 , 3766 ; 0.012)
Age <70 (n=2271)	11791 (7439)	13005 (8512)	1214 (554 , 1873 ; 0.000)
Age ≥ 70 (n=831)	15175 (13800)	16186 (14568)	1011 (-925 , 2976 ; 0.306)
Off-pump (n=1259)	12826 (12201)	13449 (10958)	623 (-660 , 1906 ; 0.341)
On pump (n=1819)	12732 (7628)	14307 (10202)	1575 (745 , 2404 ; 0)
No prior MI (n=1800)	12617 (9931)	13418 (10256)	801 (-137 , 1740 ; 0.094)
Prior MI (n=1300)	12850 (9452)	14449 (10911)	1599 (490 , 2708 ; 0.005)
NYHA class I & II (n=2431)	12774 (9968)	13690 (9769)	916 (128 , 1703 ; 0.023)
NYHA class III & IV (n=669)	12513 (8751)	14361 (12852)	1849 (166 , 3532 ; 0.031)
CCS class 0 , I , II (n=2143)	12796 (10250)	13633 (10047)	837 (-27 , 1701 ; 0.058)
CCS class III, IVa/b/c (n=959)	12537 (8387)	14291 (11525)	1754 (470 , 3038 ; 0.007)
UK (n=2053)	12985 (11334)	13838 (10817)	853 (-107 , 1812 ; 0.082)
Poland (n=606)	11489 (4443)	12319 (5519)	830 (9 , 1650 ; 0.048)
Australia (n=192)	14744 (6265)	16066 (8709)	1322 (-843 , 3486 ; 0.23)

* No tests for interaction between subgroup and treatment allocation were statistically significant

DISCUSSION

This analysis was an integral part of the ART Trial, the largest randomised comparison of bypass grafting using single (SIMA) or bilateral (BIMA) mammary arteries. Our comprehensive results show that around 70% of the additional costs observed in the BIMA arm at 12 months (£791, 95% CI £333 to £1,248, p=0.001) were incurred during the initial inpatient episode, mainly due to longer time in theatre and on hospital wards. Treatment costs associated with a small increase in sternal wound problems were significant but not sizeable. Other inpatient resource use and clinical events were similar across both trial arms.

Post-hospital discharge, and with the exception of the costs of sternal wound problems at six weeks, there were few differences between the two trial arms to 12

months. The absence of manifestations of surgery-related complications requiring treatment in the BIMA arm over this period is reassuring. Any signs of the hypothesised benefits of BIMA - sustained graft patency leading to a reduction in repeat revascularisation, lower use of anti-anginal medication, and improved survival - are only likely to become evident in the longer term. Previous trial-based studies of the cost-effectiveness of CABG versus percutaneous transluminal coronary angioplasty (PTCA) have consistently found that differences in costs arising from repeat revascularisation and medication use take time to emerge; in the SYNTAX trial these emerged over 5 years and increased when simulated over a lifetime;(12) in BARI differences did not emerge until after 12 months and persisted for at least 7 years.(13) Differences between BIMA and SIMA may take even longer to appear due to the good long-term graft patency already achievable with SIMA, and a full analysis of costs, outcomes and cost-effectiveness is planned at the primary ART endpoint of 10 years.

Exploratory sub-group analyses suggested that the incremental costs of BIMA over SIMA at 12-months could be around £1300 higher for diabetic patients as compared with non-diabetic patients, incurred mainly following hospital discharge. However, there was no evidence of interaction between subgroup and treatment allocation.

Diabetes and BIMA have been reported as independent risk factors for deep sternal wound infection following CABG in a number of observational studies performing multivariate analyses.(14, 15) However a recent study including 1,526,360 CABG patients treated in the US reported that whilst diabetes mellitus was an independent predictor of deep sternal wound infection, BIMA was not, and was only associated with an increased risk of DSWI in patients with chronic

complications of diabetes mellitus.(16) We found that, during the initial inpatient admission, the higher mean cost per patient of treatment for sternal wound problems in the BIMA arm compared to SIMA was more pronounced amongst diabetic than non-diabetic patients, although the absolute costs involved were relatively small. This pattern was even stronger for sternal wound problems occurring between discharge and 6 weeks (Supplementary Table 4).

We found some evidence that the BIMA versus SIMA difference in cost was greater for on-pump patients: a £1,575 excess compared to £623 for off-pump patients. This appears to be driven by the BIMA group: within the SIMA group, off-pump and on-pump patients appeared to have very similar costs, although the non-randomised comparison could be confounded, and there was no evidence of interaction between subgroups and treatment allocation.

The main advantage of our study is the randomised comparison, which greatly reduces the risk of unobserved bias. The retrospective database analysis by Itagaki and colleagues had a very large sample size, but it is impossible to be sure that reported differences between SIMA and BIMA were not confounded by other variables; thus, they report a shorter length of stay for BIMA versus SIMA (9.0 versus 8.0 days) and lower costs ($85,246 versus $92,698), both in the opposite direction to our findings.(16)

Limitations of our study include the fact that we have applied UK-based unit costs to resource use information from all 7 countries in the study, rather than applying local costs by centre and country and then applying an estimation model. Differences in patterns of care between countries may reflect different relative prices: for example cost differences between BIMA and SIMA related to the initial inpatient admission were highly significant for Poland but not significant for UK and Australia

(all with BIMA more costly), while initial surgery costs were lower for BIMA in Australia but significantly higher for BIMA in UK and Poland, and costs of healthcare contacts (GP etc.) were lower for BIMA than SIMA in Australia but higher in UK and Poland. However, these differences were mainly not statistically significant, total cost differences between BIMA and SIMA at 12 months were in the same direction for all countries, and there was no evidence of interaction between subgroups and treatment allocation.

CONCLUSIONS

At 12 months from randomisation, mean costs were higher in BIMA than SIMA patients, primarily due to longer time in theatre and in-hospital stay, and slightly higher costs related to sternal wound problems. Follow-up to the primary trial endpoint of 10 years is continuing, and will reveal whether longer-term differences emerge in graft patency or in overall survival.

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