Outcomes following surgical revascularisation with single versus bilateral internal thoracic arterial grafts in patients with left main coronary artery disease undergoing coronary artery bypass grafting: insights from the EXCEL trial

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ABSTRACT

Objectives

Observational data suggest that the use of a single internal thoracic artery (SITA) may result in inferior outcomes compared with bilateral internal thoracic artery (BITA) use for coronary artery bypass grafting (CABG)—a finding not yet supported by randomized trial outcomes. However, the optimal number of internal thoracic artery grafts in patients with left main coronary artery disease has not been investigated.

Methods

The EXCEL trial randomized 1905 patients with left main coronary artery disease to percutaneous coronary intervention with everolimus-eluting stents versus CABG. Among the 905 patients undergoing CABG, 688 (76.0%) received SITA and 217 (24.0%) received BITA. Differences in clinical event rates were estimated using the Kaplan-Meier method and compared with the log-rank test. Multivariable Cox regression was used to adjust for differences in baseline covariates.

Results

Compared to SITA, patients treated with BITA were younger (66.1 ± 9.5 vs 64.5 ± 9.3 years, $P = 0.020$), were less likely female (24.3% vs 14.3%, $P = 0.002$) and diabetic (28.8% vs 15.2%, $P < 0.001$), and had a lower prevalence of peripheral vessel disease (10.2% vs 5.5%, $P = 0.040$). The unadjusted 3-year composite primary endpoint of death, stroke or myocardial infarction (MI) occurred in 15.6% of SITA vs 11.6% of BITA patients ($P = 0.17$). The SITA group tended to have a higher 3-year rate of all-cause death compared with the BITA group (6.7% vs 3.3%; $P = 0.070$). Stroke, MI and ischaemia-driven revascularisation outcomes were not significantly different between groups. After adjusting for baseline differences, neither the composite of death, stroke or MI [hazard ratio (HR) 1.12, 95% confidence interval (CI) 0.71–1.78; $P = 0.62$] nor mortality (HR 1.36, 95% CI 0.60–3.12; $P = 0.46$) was significantly higher with SITA. The rehospitalization rate after 3 years was higher in the SITA group (35.8% vs 26.0%, P = 0.008), a difference which was no longer present after multivariable adjustment (HR 1.27, 95% CI 0.93-1.74; P=0.13). Sternal wound dehiscence within 30days did not occur more often in the BITA group compared to the SITA group (1.8% vs 2.2%, P>0.99).

Conclusions

In the EXCEL trial, there were no clinical differences at 3years between SITA or BITA revascularisation in patients with left main coronary artery disease.

Keywords

Coronary artery bypass grafting, Left main coronary artery disease, Bilateral internal thoracic artery, Mortality, Sternal, wound infection, EXCEL

INTRODUCTION

According to European and North American guidelines, coronary artery bypass grafting (CABG) is the treatment of choice for most patients with complex coronary artery disease.[1–4] However, with improvements in stent technology and advances in medical therapy, contemporary randomized trials have shown that percutaneous coronary intervention (PCI) with drug-eluting stents is an alternative for selected patients with left main coronary artery disease (LMCAD).[5–54]

In complex revascularisation procedures, the choice of techniques for both PCI and CABG may substantially affect clinical outcomes. In this regard, whether CABG should be performed using multiple arterial grafts or with the use of a single internal thoracic artery (SITA) in combination with saphenous vein grafts is still a matter of debate.[54–58] Pooled analyses of observational studies suggest that the use of multiple internal thoracic artery grafts results in better long-term outcomes with decreased mortality and lower rates of repeat revascularisation and myocardial infarction (MI).[54, 58–64] However, randomized trials have not yet demonstrated improved survival with the use of the bilateral internal thoracic artery (BITA).[64] Moreover, sternal wound infection and dehiscence may be increased with the use of BITA (especially in diabetic patients), resulting in low adoption rates of BITA for coronary revascularisation.[64, 64]

The EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial demonstrated that PCI was non-inferior to CABG for the composite endpoint of death, stroke or MI in patients with LMCAD and low or intermediate Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) scores.[64] The aim of the present analysis was to evaluate the safety and effectiveness of CABG with SITA versus BITA in patients with LMCAD in the EXCEL trial.[64]

METHODS

Study design

The design of the EXCEL trial has been reported previously.[68] In the EXCEL study, 1905 LMCAD patients with a SYNTAX score of 32 or lower were randomized between PCI (n = 948) and CABG (n = 957). Of the 957 randomized CABG patients, 17 patients did not undergo revascularisation. CABG was the first procedure in 923 patients and PCI in 17 patients. Eleven CABG patients (1.1%) underwent coronary revascularisa-

tion with venous grafts only. Information on the use of conduit was unavailable in 7 patients (0.7%). This *post hoc* analysis was therefore performed on the remaining 905 CABG patients in whom 1 or 2 internal thoracic artery grafts were used. Follow-up is ongoing over a period of 5years. At the time of the present report, all the patients had reached the 3-year follow-up. Adverse events were monitored and adjudicated by an independent clinical events committee. The study was performed under the supervision of the US Food and Drug Administration and by local ethics committees, and it is consistent with the Declaration of Helsinki. All the patients signed informed consent prior to the randomization.

Endpoints

The primary endpoint was the composite of all-cause death, stroke or MI at 3years. Major secondary endpoints were the primary endpoint at 30days and the composite of all-cause death, stroke, MI or ischaemia-driven revascularisation at 3 years. Additional endpoints included the components of the primary and secondary endpoints, sternal wound dehiscence, unplanned hospitalization and bleeding complications according to the Bleeding Academic Research Consortium (BARC) scale.[69]
The definitions of these endpoints have been described previously.[64, 68]

Coronary artery bypass grafting techniques

The goal of CABG was complete anatomical revascularisation of all the vessels with a diameter of 1.5 mm or larger and with an angiographic diameter stenosis of 50% or more. Although the configuration of bypass grafts was left to the discretion of the individual surgeon, the use of arterial grafts was strongly recommended. CABG could be performed with or without the support of cardiopulmonary bypass, depending on the expertise of the centre.

Statistical analyses

This *post hoc* analysis was performed in the SITA versus BITA as-treated cohorts. Discrete variables were expressed as percentages with frequencies, and they were compared by the χ^2 test or the Fisher's exact test when the expected frequency in any cell is <5. Continuous variables were summarized as mean ± SD, and they were compared by independent samples t-test if normally distributed or the Wilcoxon rank-sum test if non-normally distributed. The unadjusted cumulative event rates up to 3 years were estimated according to the Kaplan-Meier method, and differences between SITA and BITA were assessed using the log-rank test. Adjusted comparisons between SITA and BITA for the prespecified primary and secondary endpoints were performed by the complete-case multivariable Cox regression analysis accounting for the following covariates based on clinical relevance and a P-value <0.20 [70] in

univariable analyses: age, sex, body mass index >30kg/m^2 (e.g. obese), prior MI, medically treated hypertension, prior stroke or transient ischaemic attack, critical preoperative state, prior anaemia, diabetes mellitus, peripheral vascular disease, history of carotid artery disease and SYNTAX score (as a continuous variable). Patients who were missing any 1 of the covariates were not included in the multivariable model. We assessed the validity of the proportional hazards assumption by testing a time-dependent interaction between SITA versus BITA and survival time. There was no evidence that the proportionality assumption was violated. The complete Cox Regression model on the primary outcome (death, stroke or MI) is presented in **Supplementary Material**, **Table S1.**[20]

To account for missing data, we conducted separate sensitivity analyses using multiple imputations and generated 40 imputed datasets. The imputation models included the same set of covariates from our multivariable Cox regression models. All statistical tests were 2-sided, and P<0.05 was considered as statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

Among the 905 study patients undergoing CABG, 688 (76.0%) underwent SITA and 217 (24.0%) underwent BITA. In the SITA group, 10 patients withdrew consent (1.5%) and 23 patients were lost to follow-up (3.3%), whereas in the BITA group 3 patients withdrew consent (1.4%) and 4 patients were lost to follow-up (1.8%). Compared to patients treated with SITA, those receiving BITA were younger, were less commonly female, had less medically treated diabetes and peripheral vascular disease, and presented less frequently with a critical preoperative state (Table **1**). Anatomic complexity, as assessed by the SYNTAX score reported on-site, was similar between the 2 groups.

Table 1. Baseline characteristics: reported on-site

Characteristics, % (n/N)	SITA (N = 688)	BITA (N = 217)	P-value
Age (years)	66.1 ± 9.5	64.5 ± 9.3	0.020
Female sex	24.3(167)	14.3 (31)	0.002
CAD risk factors			
Medically treated hypertension	76 (523)	67.3 (146)	0.010
Hyperlipidaemia	69.5 (477/68)	67.7 (147)	0.62
Medically treated diabetes mellitus	28.8 (198)	15.2 (33)	<0.001
Cigarette use	63.2 (431/682)	62.0 (134/216)	0.76
Family history of CAD	63.7 (369/579)	67.4 (124/184)	0.37

Table 1. Baseline characteristics: reported on-site (*continued*)

Characteristics, % (n/N)	SITA (N = 688)	BITA (N = 217)	P-value
Preoperative risk factors			
Prior stroke or TIA	8.0(55)	4.6 (10)	0.090
Prior myocardial infarction[a]	15.2(104/685)	11.5 (25)	0.18
Dialysis	0.4 (3)	0.0 (0)	>0.99
PVD	10.2 (70/684)	5.5 (12)	0.040
Congestive heart failure	6.6 (45/685)	5.1 (11)	0.42
COPD	9.2 (63/687)	6.0 (13/216)	0.15
Carotid artery disease history	9.8 (67/685)	4.6 (10)	0.020
BMI (kg/m^2)	29.0 ± 5.1	28.2 ± 4.1	0.24
<20: cachectic	1.2 (8)	0.9 (2)	0.99
>30: obese	34.5 (237)	28.1 (61)	0.080
Critical preoperative state[b]	2.6 (18)	0(0)	0.010
Prior history of anaemia	10.6 (73/686)	3.7(8)	0.002
Coronary dominance			
Right	91.7 (626/683)	85.1 (177/208)	0.006
Left	8.3 (57/683)	14.9 (31/208)	0.006
LM stenosis locations			
Ostial	38.4 (264)	31.3 (68)	0.060
Mid	19.2(132)	16.1 (35)	0.31
Distal	50.9 (350)	54.8 (119)	0.31
Bifurcation	30.7 (211)	35.9 (78)	0.15
LM stenosis degree (%)			
0–<50	0.4 (3/686)	0.5 (1)	>0.99
≥50–<70	16.2 (111/686)	18.9 (41)	0.35
≥70	83.4 (572/686)	80.6 (175)	0.35
Total SYNTAX score, mean ± SD (*N*)	20.4 ± 6.3 (687)	20.7 ± 5.6 (217)	0.39
LVEF (%), mean ± SD (*N*)	57.0 ± 8.8 (663)	59.0 ± 9.6 (202)	0.0006

Values are shown as mean ± SD or frequencies in % (*n*), unless otherwise noted. The number of patients in each group is provided as SITA (*N* = 688) and BITA (*N* = 217), unless otherwise noted.

[a] Prior myocardial infarction within 2 months.

[b] Clinical preoperative state: ventricular tachycardia, ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anaesthetic room, preoperative inotropes or IABP and preoperative acute renal failure (anuria or oliguria <10 ml/h).

BITA: bilateral internal thoracic artery; BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; IABP: intra aortic balloon pump; LM: left main; LVEF: left ventricular ejection fraction; PVD: peripheral vascular disease; SD: standard deviation; SITA: single internal thoracic artery; SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; TIA: transient ischaemic attack.

Surgical characteristics

No differences were observed between the SITA and BITA groups with respect to the average number of vessels bypassed per patient or the number of conduits per patients. BITA patients had more distal anastomosis to the ramus circumflex artery yet similar rates were observed for the left anterior descending and right coronary artery (Table 2). Total arterial revascularisation was performed in 12.5% of patients

Table 2. Surgical characteristics

Characteristics	SITA (N = 688)	BITA (N = 217)	P-value
Average number of conduits per patient (arterial or venous), *n* ± SD	2.6 ± 0.8	2.6 ± 0.7	0.58
Number of vessels bypassed per patient, *n* ± SD	2.2 ± 0.6	2.3 ± 0.5	0.47
Site of distal anastomosis			
LAD	98.4 (676/687)	100.0 (217)	0.080
LCx	87.2 (599/687)	93.1 (202)	0.020
RCA	38.6 (265/687)	35.5 (77)	0.41
LAD and LCx	86.0 (591/687)	93.1 (202)	0.006
Off-pump CABG	28.6 (197)	34.1 (74)	0.13
Cardioplegia			
Crystalloid	29.9 (146/489)	23.8 (34/143)	0.16
Blood	66.9 (327/489)	71.3 (102/143)	0.32
Any blood product transfusion	4.4 (30)	2.3 (5)	0.17
Bypass duration time, min ± SD	81.6 ± 44.6	87.2 ± 44.4	0.040
Cross-clamp duration, min ± SD	52.4 ± 25.9	62.1 ± 29.2	<0.001
Duration of procedure, min ± SD (*skin-to-skin time*)	188.2 ± 62.2	218.1 ± 68.9	<0.001
ITAs used			
LITA	98.7 (679)	100.0 (217)	0.12
In situ	94.4 (641/679)	92.6 (201/217)	0.34
Free	5.7 (39/679)	8.3 (18/217)	0.18
RITA	1.3 (9)	100.0 (217)	<0.0001
In situ	77.8 (7/9)	66.4 (144/217)	0.72
Free	22.2 (2/9)	33.6 (73/217)	0.72
Use of (any) radial artery	6.4 (44)	5.1 (11)	0.48
revascularisation with only arterial grafts	12.5 (86)	65.0 (141)	<0.001
Other surgical procedures performed[a]	1.9 (13)	1.8 (4)	>0.99
Intubation >48 h	2.9 (20)	2.3 (5)	0.64
Postoperative hospital duration (days)	8.1 ± 6.7	8.8 ± 8.0	0.19
Medications at discharge			
Aspirin	99.3 (672/677)	98.1 (208/212)	0.23
ACE-inhibitor or ARB	41.9 (285/680)	43.5 (93/214)	0.69
Beta blocker	93.1 (633/680)	91.6 (196/214)	0.46
Calcium channel antagonists	7.9 (54/680)	4.7 (10/214)	0.11
Statin	92.8 (631/680)	92.5 (198/214)	0.89
Any P2Y12 inhibitors	35.0 (238/680)	26.2 (56/214)	0.020
Clopidogrel	34.4 (234/680)	24.8 (53/214)	0.008
Ticagrelor	0.0 (0/680)	0.9 (2/214)	0.060
Prasugrel	0.6 (4/680)	0.0 (0/214)	0.58

Values are shown as mean ± SD or frequencies in % (*n*), unless otherwise noted. The number of patients in each group is provided as SITA (*N* = 688) and BITA (*N* = 217), unless otherwise noted.

[a] Aortic valve surgery, mitral valve surgery, tricuspid valve surgery and atrial appendage closure.

ACE: Angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; BITA: bilateral internal thoracic artery; CABG: coronary artery bypass grafting; ITA: internal thoracic artery; LAD: left anterior descending; LCx: ramus circumflex (circumflex artery); LITA: left internal thoracic artery; RCA: right coronary artery; RITA: right internal thoracic artery; SD: standard deviation; SITA: single internal thoracic artery; Skin-to-skin time: the time between the first incision until the final closing of the sternotomy wound.

in the SITA group vs 65.0% in the BITA group (P < 0.001). Radial artery grafts were used infrequently in each group.

Usage of off-pump surgery was similar between the 2 groups. Patients treated with SITA compared with BITA had shorter procedure duration times, total bypass duration times and shorter cross-clamp times (Table **2**). The postoperative hospital stay was similar in both groups.

Clinical outcomes

The 30-day clinical outcomes, including the composite rate of death, stroke or MI and ischaemia-driven repeat revascularisation, were not significantly different between the 2 groups (Table **3**). The rate of sternal wound dehiscence was comparable with SITA and BITA revascularisation (2.2% vs 1.8%, respectively; *P* > 0.99).

Table 3. Unadjusted 30-day clinical outcomes

Endpoints	SITA (N = 688), % (n)	BITA (N = 217), % (n)	Hazard ratio (95% confidence interval)	P-value
Death, stroke or MI	7.8 (54)	7.8 (17)	1.00 (0.58–1.73)	>0.99
All-cause death	0.9 (6)	1.4 (3)	0.63 (0.16–2.51)	0.51
Cardiovascular	0.9 (6)	0.9 (2)	0.94 (0.19–4.66)	0.94
Non-cardiovascular	0.0 (0)	0.5 (1)		
Stroke	1.5 (10)	0.9 (2)	1.66 (0.34–7.16)	0.56
MI	6.1 (42)	6.5 (14)	0.95 (0.52–1.73)	0.86
Ischaemia-driven revascularisation	1.3 (9)	0.9 (2)	1.41 (0.31–6.54)	0.66
Major bleeding (BARC 3–5)	9.0 (62)	8.3 (18)	1.09 (0.65–1.85)	0.74
Sternal wound dehiscence[a]	2.2 (15)	1.8(4)	1.18 (0.40–3.53)	>0.99

Rates are the Kaplan–Meier estimates (*n* events).
[a] Reported on-site.
BARC: Bleeding Academic Research Consortium; BITA: bilateral internal thoracic artery; MI: myocardial infarction; SITA: single internal thoracic artery.

At 3-year follow-up, the unadjusted rate of the primary composite endpoint of all-cause death, stroke or MI occurred in 15.6% of patients in the SITA group vs 11.6% in the BITA group (P = 0.17, Fig. **1** A and Table **4**). There was a trend towards a higher rate of all-cause death with SITA versus BITA: 6.7% vs 3.3% (Fig. **1**B), respectively (*P* = 0.070). There were no significant differences in the 3-year rates of stroke, (Fig. **1**C and D) MI, ischaemia-driven revascularisation or major bleeding complications (BARC Class 3–5) between the (Fig. **2**A and B) groups. At 3 years, SITA patients had a significantly higher rate of unplanned hospitalization compared to BITA patients (35.8% vs 26.0%, *P* = 0.008, Fig. **2**C and Table **4**). In the SITA group, 20.1% of the

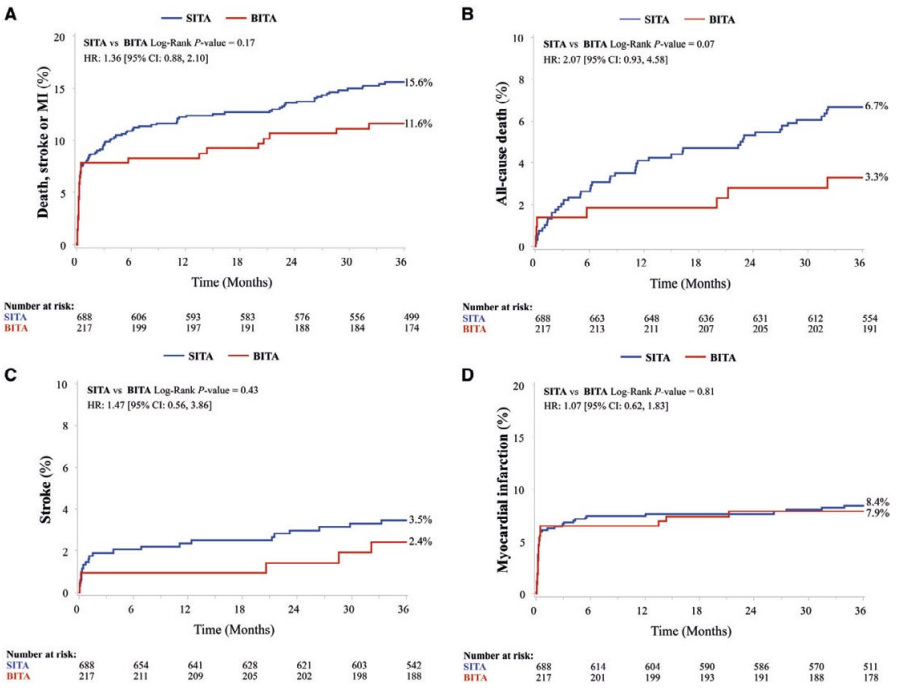

Figure 1. Kaplan–Meier curves on 3-year primary endpoints. Statistical significance is calculated with the log-rank test, and HRs with a 95% CI are provided. (A) Death, stroke or MI. (B) All-cause death. (C) Stroke. (D) MI. SITA is represented by the blue line, and BITA is represented by the red line. BITA: bilateral internal thoracic artery; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; SITA: single internal thoracic artery.

patients had a cardiovascular indication for unplanned admission compared to 13.8% of the patients in the BITA group ($P = 0.04$). After adjustment for differences in baseline covariates by multivariable Cox regression, none of the rates of the primary or secondary clinical outcomes were significantly different between the SITA and BITA groups (Table **4**). Adjusted associations were consistent after multiple imputations of missing data (**Supplementary Material**, **Table S2**).

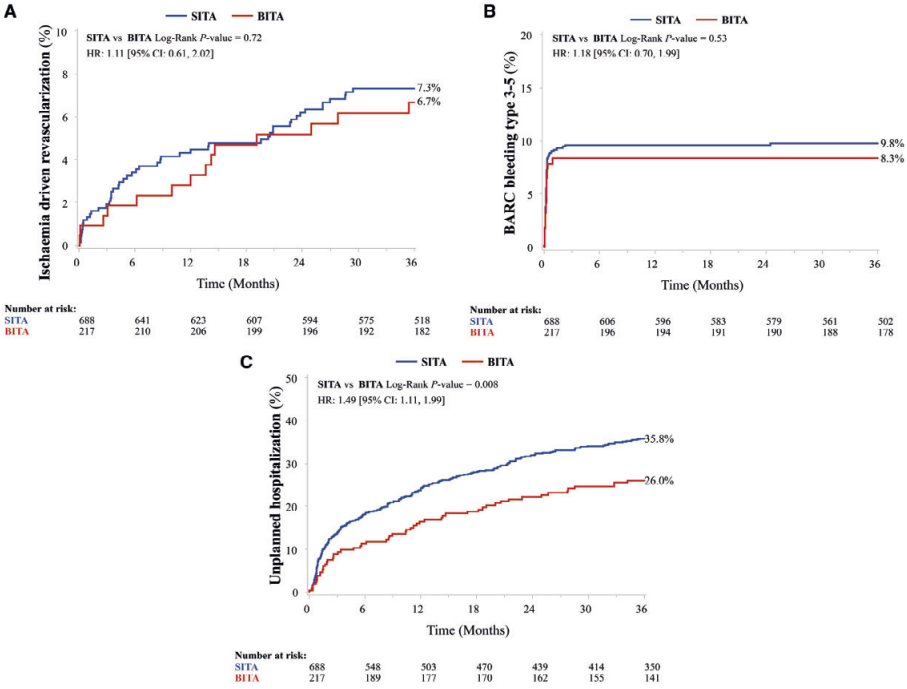

Figure 2. Kaplan–Meier curves on 3-year secondary endpoints. Statistical significance is calculated with the log-rank test, and HRs with a 95% CI are provided. (**A**) Ischaemia-driven revascularisation (**B**) BARC bleeding type 3–5. (**C**) Unplanned hospitalization. SITA is represented by the blue line, and BITA is represented by the red line. BITA: bilateral internal thoracic artery; CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; SITA: single internal thoracic artery.

Table 4. Unadjusted and adjusted 3-year clinical outcomes

Endpoints	SITA (N = 688), % (n)	BITA (N = 217), % (n)	Unadjusted hazard ratio (95% CI)	Unadjusted P-value	Adjusted hazard ratio (95% CI)	Adjusted P-value
Death, stroke or MI	15.6 (106)	11.6 (25)	1.36 (0.88–2.10)	0.17	1.12 (0.71–1.78)	0.62
All-cause death	6.7 (45)	3.3 (7)	2.07 (0.93–4.58)	0.07	1.36 (0.60–3.12)	0.46
Cardiovascular	4.2 (28)	2.4 (5)	1.80 (0.69–4.65)	0.22	1.14 (0.42–3.06)	0.80
Non-cardiovascular	2.6 (17)	0.9 (2)	2.74 (0.63–11.86)	0.16	1.93 (0.43–8.77)	0.39
Stroke	3.5 (23)	2.4 (5)	1.47 (0.56–3.86)	0.43	0.88 (0.32–2.43)	0.80
MI	8.4 (57)	7.9 (17)	1.07 (0.62–1.83)	0.81	1.04 (0.58–1.85)	0.90
Ischaemia-driven revascularisation	7.3 (48)	6.7 (14)	1.11 (0.61–2.02)	0.72	1.02 (0.54–1.93)	0.96
Major bleeding (BARC 3–5)	9.8 (67)	8.3 (18)	1.18 (0.70–1.99)	0.53	1.12 (0.64–1.94)	0.39
Unplanned hospitalization	35.8 (238)	26.0 (55)	1.49 (1.11–1.99)	0.008	1.27 (0.93–1.74)	0.13

Rates are the Kaplan-Meier estimates
(*n* events).
BARC: Bleeding Academic Research Consortium; BITA: bilateral internal thoracic artery; CI: confidence interval; MI: myocardial infarction; SITA: single internal thoracic artery.

DISCUSSION

Due to the absence of significant differences in the postoperative outcomes such as all-cause death, stroke, MI or sternal wound dehiscence between BITA and SITA surgical revascularisation in patients with LMCAD and low to intermediate SYNTAX scores, one can conclude that the use of BITA was equally safe compared to the use of SITA at the 3-year follow-up.

A potential reason for the less frequent use of BITA could be the risk of competitive coronary flow on arterial grafts. Sabik *et al.* [71] showed that when the degree of preoperative proximal stenosis decreases to below mild (<40%), the risk of competitive coronary flow for arterial grafts increases and thereby compromising graft patency. Yet, in the current study, over 99% of both SITA and BITA patients had a moderate-to-severe left main coronary artery stenosis, of whom over 80% had a severe (≥70%) left main stenosis (Table **1**). Furthermore, patients undergoing BITA compared to SITA were younger and had fewer comorbidities, possibly due to the selection bias of BITA

patients having a more favourable life-expectancy and better clinical status. This resulted in less favourable 3-year outcomes in unadjusted analyses. However, after multivariable adjustment for these covariates, event-free survival and the individual rates of adverse events, including all-cause death, were comparable with both types of revascularisation. Specifically, no significant differences were observed for the individual endpoints of death, stroke, MI, ischaemia-driven repeat revascularisation, unplanned hospitalization, bleeding complications or sternal wound dehiscence.

The EXCEL trial recommended performing total arterial coronary revascularisation in an effort to ensure complete revascularisation with the highest possible graft patency rates.[54] The most commonly used grafts were the internal thoracic arteries, which were used in 99.0% of patients. Radial artery grafts were used in only 5.1% of patients in the BITA group and 6.4% of patients in the SITA group, and the gastroepiploic artery was not used at all. Despite the protocol recommendations and inclusion of highly skilled sites in the EXCEL trial, only 24.0% of patients underwent BITA, and complete arterial revascularisation was achieved in only 25.1% of all patients. The results of this study thus demonstrate that bilateral arterial grafts and complete arterial revascularisation are not frequently used in contemporary surgical practice.

Intubation and duration of the initial hospitalization were not prolonged in the BITA group. Although the use of BITA prolonged the procedure compared with SITA, the use of BITA was reassuringly safe with nearly identical 2% rates of sternal wound dehiscence in both the groups. Nonetheless, there were no significant differences in 30-day or 3-year clinical outcomes between patients treated with SITA and BITA. The higher rate of unplanned hospitalizations in the SITA group was likely due to the higher prevalence of comorbidities as this risk was no longer present after the adjustment for clinically relevant covariates. Similarly, the ART trial (n = 3102), the largest randomized trial to date with 10-year survival as a primary endpoint, did not demonstrate a difference in mortality or other adverse events in the interim analysis at 5 years with BITA compared with SITA,[64] and the sternal wound complication rate was slightly higher in the BITA group (3.5% vs 1.9%). However, the 3- to 5-year follow-up from the EXCEL and ART trials may be too short for the benefits of BITA to emerge. In a meta-analysis of observational studies, Yi *et al.* [72] reported a survival benefit of BITA compared with SITA when follow-up was extended to ≥9 years. The observational study from the Cleveland Clinic by Lytle *et al.* [73] followed patients up to 20 years and showed that BITA and SITA survival curves only started to diverge in favour of BITA revascularisation at 10-year follow-up. CABG with BITA revascularisation may therefore be encouraged, considering the outcomes of current study with

respect to the unequivocal long-term survival benefits of BITA, which is reported by observational studies and meta-analysis.[72, 73]

It is noteworthy that in the current study, 26.3% of the 707 male patients and 15.6% of the 198 female patients received BITA revascularisation. While the reasons for the lower rates of BITA use in women are not immediately apparent, these rates are similar to previous studies [75] and emphasize the need for future research in women undergoing cardiac surgery.[25, 74]

In addition to longer-term follow-up from the EXCEL and ART trials, insights into the outcomes of BITA compared to SITA will be gained from the recently initiated ROMA trial, in which more than 4000 patients undergoing CABG were randomized into two groups receiving either single or multiple arterial grafts, with follow-up planned for up to 10 years.[76]

Limitations

The present study with 905 patients is modest in size, but nonetheless represents the largest analysis to date on the use of BITA versus SITA in patients with LMCAD undergoing surgical revascularisation. The BITA and SITA groups were not randomized, and patients in the BITA group had fewer comorbidities, requiring multivariable adjustment. However, we cannot exclude the role of unmeasured confounders, and thus these results should be considered hypothesis-generating. The reasons for performing BITA versus SITA were not prospectively collected. Further insights may be obtained with longer-term follow-up from the EXCEL trial (presently planned for 5 years). Finally, EXCEL excluded patients with high anatomic SYNTAX scores assessed by local heart teams (e.g. SYNTAX score >33), and thus the results do not apply to patients with highly complex LMCAD. The recently published systematic review by Head *et al.* [78] showed a larger survival benefit of CABG over PCI in patients with intermediate to complex multi-vessel disease (SYNTAX score ≥ 23), which was not found in complex LMCAD patients.

CONCLUSIONS

In the EXCEL trial, CABG with SITA versus BITA revascularisation for patients with LMCAD resulted in no significant differences in the rate of the primary composite endpoint of death, stroke or MI at 3years, or in any of the individual endpoints at 30days or 3 years, including bleeding complications, ischaemia-driven revascularisation or unplanned hospitalization. As there were also no differences in sternal

wound dehiscence rates between SITA and BITA revascularisation, the use of BITA can be considered safe. Longer-term follow-up (for ≥10 years) should be performed to completely characterize the potential impact of SITA versus BITA revascularisation on long-term outcomes after CABG in high-risk patients with LMCAD.

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SUPPLEMENTARY MATERIAL

Supplementary material is also available at *EJCTS* online.

SUPPLEMENTARY MATERIAL

Table S1. Full Cox Regression model on the primary outcome (death, stroke or MI).

Variable	Hazard ratio [95% CI]	*P*-value
SITA vs BITA	1.12 [0.71 – 1.78]	0.62
Age, per 5 years	1.03 [0.84 – 1.26]	0.77
Sex, male vs female	1.04 [0.67 – 1.61]	0.86
BMI, >30 vs ≤30 kg/m^2	0.98 [0.67 – 1.46]	0.98
Prior MI	1.02 [0.64 – 1.63]	0.93
Medically-treated hypertension	1.31 [0.82 – 2.08]	0.25
Prior stroke or TIA	1.14 [0.60 – 2.16]	0.69
Critical preoperative state	0.76 [0.18 – 3.15]	0.71
Diabetes mellitus	1.29 [0.87 – 1.91]	0.21
Peripheral vascular disease	0.45 [0.22 – 0.94]	0.03
COPD	2.51 [1.54 – 4.09]	<0.001
Prior anemia	1.52 [0.89 – 2.61]	0.13
History of carotid artery disease	1.69 [0.93 – 3.06]	0.08
SYNTAX score, per 5 units	1.02 [0.93 – 1.12]	0.66

Here, the full Cox Regression Model on the primary outcome (death, stroke or MI) is reported according to the EJCTS Statistical and Data Reporting Guideline.[20] Of note, there were no changes to the treatment effect inferences when "critical preoperative state" and "peripheral vascular disease" were eliminated from the model. A BMI of > 30 is classified as obese.

Abbreviations used: SITA: single internal thoracic artery, BITA: bilateral internal thoracic artery, BMI: Body Mass Index, MI: myocardial infarction, TIA: transient ischemic attack, COPD: chronic obstructive pulmonary disease, SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

Table S2. Multivariable adjusted three-year clinical outcomes after multiple imputations.

Endpoint	Hazard ratio [95% CI] (adjusted)	Adjusted *P*-value
Death, stroke or MI	1.22 [0.77 – 1.93]	0.40
All-cause death	1.52 [0.66 – 3.49]	0.32
Cardiovascular	1.34 [0.49 – 3.66]	0.57
Non-cardiovascular	1.99 [0.47 – 8.44]	0.35
Stroke	1.14 [0.40 – 3.23]	0.80
MI	1.09 [0.62 – 1.94]	0.76
Ischemia-driven revascularization	0.99 [0.53 – 1.86]	0.99
Major bleeding (BARC 3-5)	1.08 [0.64 – 1.83]	0.78
Unplanned hospitalization	1.28 [0.95 – 1.73]	0.11

Hazard ratios with 95% confidence intervals, for SITA versus BITA, were calculated after adjustment for differences in baseline covariates by multivariable Cox regression and multiple imputations.
Abbreviations used: SITA: single internal thoracic artery, BITA: bilateral internal thoracic artery, MI: myocardial infarction, BARC: Bleeding Academic Research Consortium.