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Does the use of bilateral mammary artery grafts compared with the use of a single mammary artery graft offer a long-term survival benefit in patients undergoing coronary artery bypass surgery?

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Abstract

A best evidence topic in cardiac surgery was written according to a structured protocol. The question addressed was: 'Does the use of bilateral mammary artery grafts compared with the use of a single mammary artery graft offer a long-term survival benefit in patients undergoing coronary artery bypass surgery?' Altogether 214 papers were found using the reported search, of which 13 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. All the included studies were follow-up studies; eight studies used prospective data collection, and five studies collected the study data retrospectively. No randomized controlled trials were found. Nine of the 13 included papers used a propensity-score-matched comparison of the survival of bilateral mammary artery graft [or, bilateral internal thoracic artery (BITA) graft] patients vs single mammary artery graft [or, single internal thoracic artery (SITA) graft] patients. These studies consistently showed an enhanced survival of BITA patients compared with propensity-score-matched SITA patients. Three of the 13 included papers used Cox proportional hazards regression analysis to compare survival of BITA vs SITA patients; one larger study showed better crude survival of BITA patients, but did not identify BITA grafts as independent predictor of enhanced survival. The remaining two studies also did not identify BITA grafts as independent predictor of enhanced survival. One study only presented crude survival estimates of BITA vs SITA patients and therefore was of limited informative value. We conclude that the use of BITA grafts seems to offer a long-term survival benefit compared with a SITA graft for patients undergoing coronary artery bypass grafting surgery. Although randomized evidence is lacking, observational evidence supporting this hypothesis is mounting.

Keywords: Review • Coronary artery bypass grafting • Bilateral internal mammary artery • Survival

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the *ICVTS* [1].

THREE-PART QUESTION

In patients undergoing coronary bypass grafting surgery, is the use of bilateral mammary artery bypass grafts superior to the use of a single mammary artery bypass graft in terms of long-term survival?

CLINICAL SCENARIO

You are scheduled to perform an elective coronary bypass grafting procedure and discuss the case with your resident the night before. You plan to revascularize the anterior wall with the left internal mammary artery (LIMA), and discuss the possibilities of revascularization of the lateral and inferior wall with your resident. He suggests using a second mammary artery graft. You ask him to do a literature search on the latest research on long-term survival of this procedure compared with the use of a saphenous vein graft (SVG).

SEARCH STRATEGY

Medline (PubMed interface) was searched from 1950 until January 2013, using the following criteria: 'Coronary Artery Bypass'[Mesh] AND 'bilateral mammary artery' AND 'Mortality'.

SEARCH OUTCOME

Two hundred and fourteen papers were found using the reported search. Two authors (T.S. and G.T.L.K.) independently assessed all the papers and selected 13 papers that provided the best evidence to answer the question. These are presented in Table 1. We used the meta-analysis performed in 2001 by Taggart *et al.* [2] as a starting point and thus excluded all papers that were published

Table 1: Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Grau *et al.* (2012), Eur J Cardiothorac Surg [3], USA Prospective follow-up study Comparison of propensity-score-matched groups (level IIa)	Elective CABG patients: BITA *n* = 1459, SITA (LIMA + SVG) *n* = 4854 Propensity-score-matched groups: BITA *n* = 928, SITA *n* = 928 Mean follow-up 9 ± 0.5 years	15-year survival	BITA 79% vs SITA 61%, *P* < 0.0001	Enhanced long-term survival of BITA patients, compared with propensity-score-matched SITA patients
Galbut *et al.* (2012), J Thorac Cardiovasc Surg [4], USA Prospective follow-up study Comparison of propensity-score-matched groups (level IIa)	Elective and non-elective CABG patients, stratified by LVEF: BITA *n* = 2197, SITA *n* = 2340	Long-term survival, LVEF < 30%	7 years: BITA 51.7 ± 5.4% vs SITA 57.0 ± 5.3% 14 years: BITA 26.6 ± 5.5% vs SITA 26.6 ± 5.1% *P* = 0.934	Enhanced long-term survival of BITA patients compared with propensity-score-matched SITA patients, with normal or reduced ejection fraction, but not in patients with EF < 30%
		Long-term survival, LVEF 30–50%	10 years: BITA 62.0 ± 2.3% vs SITA 57.7 ± 2.3% 20 years: BITA 33.1 ± 3.4% vs SITA 19.2 ± 2.5% *P* = 0.016	
		Long-term survival, LVEF > 50%	14 years: BITA 59.4 ± 1.5% vs SITA 54.4 ± 1.5% 28 years: BITA 19.5 ± 3.4% vs SITA 14.4 ± 4.2% *P* = 0.012	
Locker *et al.* (2012), Circulation [5], USA Retrospective follow-up study Comparison of propensity-score-matched groups and adjustment for differences between groups by Cox model (level IIa)	Isolated primary CABG patients BITA/SVG *n* = 589, BITA-only *n* = 271, BITA/RA *n* = 147, LITA/RA *n* = 169, BITA/RA/SVG *n* = 8, RITA/RA *n* = 2, BITA/GEA *n* = 1	Multiple arterial grafts (i.e. BITA, BITA/RA, LITA/RA) vs SITA, propensity-score-matched survival	Multiple arterial grafts 83 and 70% vs SITA 80 and 60% at 10- and 15-year follow-up, respectively, *P* = 0.0025	BITA grafts conferred a survival benefit at 15 years compared with SITA grafts
		15-year survival BITA-only vs SITA (crude Kaplan–Meier estimates)	BITA 74.5% (95% confidence interval (CI) 63.1–88.1%) vs SITA 36.3% (95% CI 34.6–38.1%)	
		15-year survival BITA/SVG vs SITA (crude Kaplan–Meier estimates)	BITA 75.8% (95% CI 69.8–82.3%) vs SITA 36.3% (95% CI 34.6–38.1%)	
		Adjusted survival benefit BITA-only vs SITA (Cox model)	Hazard ratio (HR) = 0.80 (95% CI 0.55–1.16, *P* = 0.237)	
		Adjusted survival benefit BITA/SVG vs SITA/(Cox model)	HR = 0.73 (95% CI 0.57–0.94, *P* = 0.015)	

Continued

Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Kinoshita *et al.* (2012), Ann Thorac Surg [6], Japan Prospective follow-up study Comparison of propensity-score-matched groups (level IIa)	Isolated CABG patients ages 70 years or greater SITA *n* = 247, BITA *n* = 244 Propensity-score-matched groups: 217 pairs	Propensity-matched 5-year survival estimates Adjusted survival benefit BITA vs SITA (Cox model)	BITA 86.4 ± 3.2% vs SITA 73.5 ± 3.9% (*P* = 0.01) HR = 0.56 (95% CI 0.31–0.99, *P* = 0.04)	In elderly patients, BITA grafting is associated with a lower 5-year mortality compared with SITA grafting
Kurlansky *et al.* (2010), Ann Thorac Surg [7], USA Retrospective follow-up study Comparison of propensity-score-matched groups (level IIa)	Isolated CABG patients BITA *n* = 2215, SITA *n* = 2369 Propensity-score-matched groups: BITA *n* = 2197, SITA *n* = 2197 Mean follow-up 11.5 years	Crude survival estimates at 15 years Crude survival estimates at 25 years Propensity-matched groups survival at 15 years Propensity-matched groups survival at 25 years	BITA 53.5 ± 1.2% vs SITA 37.5 ± 1.1% (*P* < 0.001) BITA 28.6 ± 2.2% vs SITA 15.7 ± 2.0% (*P* < 0.001) BITA 53.5 ± 1.2% vs SITA 39.0 ± 1.1% (*P* = 0.001) BITA 28.5 ± 2.2% vs SITA 16.5 ± 2.1% (*P* = 0.001)	BITA grafting offers a long-term survival advantage over SITA grafting
Kieser *et al.* (2011), Ann Thorac Surg [8], Canada Prospective follow-up study Adjustment for differences between groups by Cox model (level IIa)	Isolated CABG patients BITA *n* = 1038, SITA *n* = 4029 Mean follow-up 7.1 years	1-year mortality Crude survival benefit of BITA vs SITA Adjusted survival benefit BITA vs SITA (Cox model)	BITA 2.4% vs SITA 4.3% vs vein-only 8.2% HR 0.46 (95% CI 0.37–0.57, *P* < 0.0001) HR 0.87 (95% CI 0.69–1.08, *P* = 0.2). Spline analysis of plotting HR (BITA vs SITA) against age suggested potential survival benefit of BITA in patients <69.9 years of age	Better crude survival for BITA patients. However, after adjustment not significant anymore. Maybe age is an effect modifier. BITA seems reasonable in patients <70 years of age
Mohammadi *et al.* (2008), Eur J Cardiothorac Surg [9], Canada Prospective follow-up study Adjustment for differences between groups by Cox model (level IIa)	Primary isolated CABG patients BITA *n* = 1277, SITA *n* = 9566 Mean follow-up 5.7 ± 3.7 years	Crude survival (at 5, 7 and 10 years, respectively) Adjusted survival benefit BITA vs SITA (Cox model) Adjusted survival benefit per age category (Cox model)	98.4, 97.8 and 96.5% for BITA vs 96.6, 94.3 and 88.9% for SITA (*P* < 0.0001) HR = 0.02 (95% CI 0.002–0.40, *P* = 0.009) Survival benefit of BITA vs SITA gradually decreases with age, and is lost after 60 years of age	Additional survival benefit of BITA compared with SITA. This survival benefit decreases gradually with age, and is lost after 60 years of age

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Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Di Mauro *et al.* (2005), Ital Heart J [10], Italy Prospective follow-up study Comparison of propensity-score-matched groups (level IIa)	Primary CABG patients <70 years of age Propensity-score-matched groups: BITA *n* = 476, SITA *n* = 476 Mean follow-up 8.8 ± 4.0 years	10-year survival	BITA 92.4 ± 2.1%, SITA 87.5 ± 3.5%, *P* = 0.0216	BITA patients had better 10-year survival compared with propensity-score-matched SITA patients
Lytle *et al.* (2004), Ann Thorac Surg [11], USA Prospective follow-up study Comparison of propensity-score-matched groups (level IIa)	Primary CABG patients BITA *n* = 1152, SITA *n* = 1152 Mean follow-up 16.2 years	Long-term survival	BITA vs SITA, 89 vs 87%, 81 vs 78%, 67 vs 58% and 50 vs 37% at 7-, 10-, 15- and 20-year follow-up, respectively, *P* < 0.0001	BITA patients had better long-term survival compared with propensity-score-matched SITA patients
Calafiore *et al.* (2004), Eur J Cardiothorac Surg [12], Italy Prospective follow-up study Comparison of propensity-score-matched groups (level IIa)	Primary CABG patients <75 years BITA *n* = 1026, SITA *n* = 576 Propensity-score-matched pairs: BITA *n* = 570 vs SITA *n* = 570 Mean follow-up 7.3 ± 4.8 years	Propensity-matched 10-year survival 10-year freedom from cardiac death 10-year freedom from acute myocardial infarction (AMI) 10-year freedom from AMI in grafted area 10-year freedom from target cardiac events	BITA 90.5 ± 2.8 vs SITA 87.1 ± 1.6, *P* = 0.0696 BITA 96.5 ± 0.8% vs SITA 91.3 ± 1.4%, *P* = 0.0288 BITA 98.0% ± 0.6 vs SITA 94.3 ± 1.2%, *P* = 0.0180 BITA 98.4% ± 0.6 vs SITA 94.7 ± 1.1%, *P* = 0.0057 BITA 93.9 ± 1.1% vs SITA 86.3% ± 1.8, *P* = 0.0388	No significant survival benefit in propensity-matched groups of BITA vs SITA patients. BITA patients had better long-term freedom from cardiac death, as well as freedom from events
Hirotani *et al.* (2003), Ann Thorac Surg [13], Japan Retrospective follow-up study Comparison of crude survival estimates (level IIa)	Primary CABG in diabetic patients (both insulin dependent and non-insulin dependent) BITA *n* = 179, SITA *n* = 124	Long-term survival	No differences in long-term survival between BITA and SITA	No difference in long-term mortality between BITA patients and SITA patients These results should be interpreted with caution as only crude survival estimates were compared

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Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Endo *et al*. (2003), Circulation [14], Japan Retrospective follow-up study Adjustment for differences between groups by Cox model (level IIa)	Primary CABG patients, studied in subgroups of diabetic patients and non-diabetic patients Diabetic patients: BITA *n* = 190, SITA *n* = 277. Non-diabetic patients: SITA *n* = 411, BITA *n* = 253 Median follow-up 8.1 years	Crude 10-year survival among diabetic patients 10-year survival among diabetic patients with LVEF > 40% Adjusted survival benefit BITA (Cox model) among diabetic patients Adjusted survival benefit BITA (Cox model) in diabetic patients with LVEF > 40%	BITA 80.2 ± 3.8% vs SITA 75.4 ± 3.0%, *P* = 0.46 BITA 87.8 ± 3.5% vs 75.2 ± 3.4%, *P* = 0.04 HR = 0.91 (95% CI 0.597–1.4, *P* = 0.6) HR = 0.61 (95% CI 0.36–1.067, *P* = 0.08)	BITA grafting is not significantly better in reducing all-cause mortality than SITA grafting when assessing the Cox proportional hazards estimates
Endo *et al*. (2001), Circulation [15], Japan Retrospective follow-up study Adjustment for differences between groups by Cox model (level IIa)	Isolated CABG patients BITA *n* = 443, SITA *n* = 688 Median follow-up 6.15 years	7-year all death-free rate 7-year re-CABG free rate Adjusted survival benefit BITA vs SITA (Cox model)	BITA 88.7 ± 1.9% vs SITA 86.9 ± 1.4%, *P* = 0.6 BITA 99.5% vs SITA 97.3%, *P* = 0.0256 HR = 0.95, 95% CI 0.67–1.35	No differences in mortality between BITA and SITA patients

Survival data are presented as Kaplan–Meier survival estimate ± standard error of the mean, or as Kaplan–Meier survival estimate with corresponding 95% CI. AMI: acute myocardial infarction; BITA: bilateral internal thoracic artery; CABG: coronary artery bypass grafting; CI: confidence interval; GEA: gastroepiploic artery; HR: hazard ratio; LITA: left internal thoracic artery; LVEF: left ventricular ejection fraction; SVG: saphenous vein graft; MI: myocardial infarction; RA: radial artery.

before 2001. We included studies in which at least 100 patients in each arm were followed up at least for 4 years. The variables age, sex, ventricular function and diabetes status needed to be reported for each study arm separately.

RESULTS

Grau *et al*. [3] performed a prospective follow-up study of patients undergoing elective coronary artery bypass surgery (CABG), and made 928 propensity-score-matched pairs of bilateral internal thoracic artery (BITA) vs single internal thoracic artery (SITA) patients. During a mean follow-up of 9 years, BITA patients showed to have an enhanced 15-year survival compared with propensity-score-matched SITA patients.

Galbut *et al*. [4] performed a prospective follow-up study of both elective and non-elective CABG patients and made propensity-score-matched groups. Patients were stratified by left ventricular ejection fraction (LVEF). Long-term survival was better among BITA patients with normal or reduced left-ventricular ejection fraction (respectively LVEF > 50% and LVEF 30–50%), but not among patients with a LVEF of < 30%.

Locker *et al*. [5] performed a retrospective analysis of patients undergoing CABG. At 10- and 15-years of follow-up, patients with multiple arterial grafts (i.e. BITA, BITA and radial artery (RA), or SITA and RA) had a significantly better survival compared with propensity-score-matched SITA patients. Although no separate analysis of BITA grafts (i.e. without patients receiving the combination SITA + RA) compared with propensity-score-matched SITA patients is presented, the crude survival estimates of BITA-only patients and BITA + SVG patients are both significantly better than SITA patients. Also, the Cox proportional hazards model showed that both the use of BITA-only and of BITA + SVG were associated with a significantly lower risk of early mortality compared with SITA.

Kinoshita *et al*. [6] performed a propensity-score-matched analysis in patients ≥70 years of age and showed that the use of BITA grafts is associated with significantly lower mortality at 5-years of follow-up in these patients.

Kurlansky *et al*. [7] performed a retrospective analysis of 2197 propensity-score-matched pairs of BITA and SITA patients and showed that BITA grafts offered a long-term survival benefit compared with SITA grafts (at 15- and 25-years of follow-up).

Kieser *et al*. [8] performed a prospective follow-up study showing that crude mortality was lower in BITA patients compared

with SITA patients. However, the adjusted survival benefit was non-significant. Subanalyses of the data showed that age was a potential effect modifier and that BITA grafting might offer a survival benefit in patients <70 years of age.

Mohammadi *et al*. [9] performed a prospective follow-up study of 1277 BITA patients and 9566 SITA patients. BITA grafting was associated with a significantly lower risk of early mortality, and this survival benefit seemed to be lost in patients older than 60 years of age.

Di Mauro *et al*. [10] showed in a prospective manner that BITA patients had a significant better 10-year survival compared with propensity-score-matched SITA patients.

Lytle *et al*. [11] studied 1152 propensity-score-matched pairs of BITA vs SITA patients over a mean period of 16.2 years and found that survival was significantly better among BITA patients compared with SITA patients.

Calafiore *et al*. [12] found no significant survival benefit of BITA grafting at 10-year follow-up.

Hirotani *et al*. [13] found no difference in long-term mortality between BITA and SITA patients with diabetes. However, this analysis has the limitation that only crude mortality rates were assessed in a small group of patients (BITA $n = 179$ vs SITA $n = 124$).

Endo *et al*. [14] performed a retrospective analysis among diabetic CABG patients. The data were stratified according to left-ventricular ejection fraction. At 7-years of follow-up, crude mortality rates were similar between BITA and SITA patients. Cox proportional hazards analysis showed a non-significant benefit of BITA grafts when assessing all-cause mortality. However, BITA grafts conferred a benefit when assessing the composite endpoint of death, redo coronary surgery or myocardial infarction.

In 2001, Endo *et al*. [15] found no survival benefit of BITA grafting among more than 1000 patients undergoing CABG.

CLINICAL BOTTOM LINE

Although methodological issues make head-to-head comparison difficult, observational studies suggest that the use of BITA grafts seems to offer a long-term survival benefit compared with SITA for patients undergoing CABG surgery. Although randomized evidence is currently lacking, observational evidence supporting this hypothesis is mounting.

Conflict of interest: none declared.

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BEST EVIDENCE TOPIC

eComment. Two internal mammary artery grafts are better than one

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We read with great interest the paper by Smith *et al.* regarding the long-term survival benefit of the usage of bilateral internal mammary artery (BIMA) grafts in coronary revascularization surgery [1]. They included in their results 13 follow-up studies published after 2001. However, we found one additional relevant article investigating the long-term outcomes associated with BIMA grafting compared with single internal mammary artery (SIMA) among diabetic patients [2]. We would like to take this opportunity to briefly extract the relevant information from the above-mentioned study and to add a short comment on this salient subject.

Puskas *et al.* [2] conducted a retrospective cohort analysis by extracting data from the Society of Thoracic Surgeons database at a single referral academic centre. They included a total of 3527 coronary artery bypass grafting procedures (BIMA $n = 812$, SIMA $n = 2715$). After adjustment for differences between groups by the Cox model, BIMA grafting portended a 35% reduction in the hazard of long-term death at 8 years of follow-up (adjusted hazard ratio, 0.65; 95% CI, 0.48 to 0.88, $P = 0.006$). The authors concluded that the usage of BIMA grafting provides significant benefit in late survival compared with SIMA grafting in both diabetic and non-diabetic patients. BIMA grafting should be performed whenever patient risk factors and comorbidities allow an acceptable risk of deep sternal wound infection.

As rightly outlined by the authors, all these studies are follow-up studies. However, only one randomized trial comparing these two techniques (ART Arterial Revascularization Trial) [3] is currently under way in Europe that can broaden our understanding. ART primary outcome is survival at 10 years; therefore the results should be available by 2018. Until that date the debate will continue. This uncertainty has been reflected in the rate of adoption of BIMA grafting, the rate of use of the technique varies from 4% in North America to 10% in Europe [4]. The major reasons for not using BIMA grafts are the lack of solid evidence of benefits and the increased rate of sternal wound infection, particularly in diabetics. Of note, in the SYNTAX study [5], BIMA grafting was used in a relatively higher percentage of 28% of patients.