

Off-Pump Coronary Artery Bypass Graft Surgery with Bilateral Internal Mammary Arteries in Left Main Coronary Artery Disease. Is There Any Benefit in 10-Year Mortality?

Cirugía de revascularización coronaria sin bomba con 2 arterias mamarias en la enfermedad del tronco ¿genera beneficio en la mortalidad a 10 años?

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ABSTRACT

Background: The randomized controlled trials comparing coronary artery bypass graft (CABG) surgery versus percutaneous coronary intervention (PCI) included all types of surgical techniques (on-pump and off-pump) and different conduits (arterial and venous). Is it reasonable to assume that all surgical techniques are equal in terms of late mortality?

Objectives: The aim of this study was to evaluate whether off-pump CABG surgery using both mammary arteries provides additional benefit over conventional revascularization using single mammary artery in terms of long-term survival for left main coronary artery (LMCA) disease.

Methods: We conducted a retrospective, observational and comparative study (n = 723) adjusted for risk. A stratified analysis was performed according to the use of single internal thoracic artery (SITA, n = 144) or bilateral internal thoracic arteries (BITA, n = 579) analyzing survival at 10 years after the intervention.

Results: Survival at 10 years was significantly higher in BITA group (79.0% ± 3.4% vs 67.0% ± 4.9%, log-rank test, p < 0.01). This advantage was also observed in the risk-adjusted analysis (93.0% ± 4.6 vs 69.0% ± 5.7 respectively, p = 0.03). The use of BITA was an independent predictor of 10-year survival (HR 0.57, 95% CI 0.37-0.87, p = 0.01).

Conclusion: The use of bilateral internal mammary arteries in patients with left main coronary artery disease undergoing off-pump coronary artery bypass grafting was associated with higher survival at 10 years.

Key words: Coronary Artery Bypass, Off-Pump - Coronary Artery Disease - Coronary Artery Bypass - Mammary Arteries

RESUMEN

Introducción: Los ensayos clínicos aleatorizados que compararon la cirugía de revascularización miocárdica (CRM) con la angioplastia transluminal coronaria (ATC) incluyeron todo tipo de técnicas quirúrgicas (con y sin bomba de circulación extracorpórea) y diversos conductos (arteriales y venosos). ¿Es razonable suponer que todas las técnicas quirúrgicas son iguales en términos de mortalidad tardía?

Objetivos: Evaluar si la CRM sin circulación extracorpórea y con el empleo de ambas arterias mamarias tiene un beneficio adicional a la revascularización convencional utilizando una sola arteria mamaria en términos de sobrevida a largo plazo para la enfermedad del tronco de la coronaria izquierda (TCI).

Material y métodos: Estudio observacional retrospectivo comparativo (n = 723) ajustado por riesgo. Se realizó análisis estratificado según el uso de arteria mamaria interna única (SITA, n = 144) o ambas arterias mamarias internas (BITA, n = 579). Se analizó la sobrevida a los 10 años de la intervención.

Resultados: La supervivencia a los 10 años fue significativamente mayor en el grupo en que se utilizaron ambas arterias mamarias (79,0% ± 3,4% vs 67,0% ± 4,9%, log-rank test, p < 0,01). Este beneficio también se observó en el análisis ajustado por riesgo (93,0% ± 4,6 vs 69,0% ± 5,7 respectivamente, p = 0,03). El uso de ambas arterias mamarias fue un predictor independiente de sobrevida a 10 años (HR 0,57, IC 95% 0,37-0,87; p = 0,01).

Conclusión: El uso de ambas arterias mamarias internas en pacientes con enfermedad del tronco coronario izquierdo sometidos a revascularización coronaria sin circulación extracorpórea se asoció con mayor sobrevida a los 10 años.

Palabras claves: Cirugía de revascularización coronaria - Cirugía coronaria sin bomba - Enfermedad coronaria - Puente de arteria coronaria - Cirugía con doble mamaria

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INTRODUCTION

Coronary artery bypass graft (CABG) surgery has been established as the gold standard treatment for coronary artery disease and is the standard of care to validate percutaneous coronary interventions (PCIs) in randomized clinical trials (RCTs). However, studies comparing CABG surgery versus PCI included all types of surgical techniques (on-pump and off-pump) and different conduits (arterial and venous). Is it reasonable to assume that all surgical techniques are equal in terms of long-term mortality?

There is still disagreement about which conduits are the best for CABG, particularly in left main coronary artery (LMCA) disease. Pooled data from large observational studies have demonstrated the superiority of bilateral internal thoracic artery (BITA) versus single internal thoracic artery (SITA) (1) for multivessel coronary artery disease. Although these studies included patients with LMCA disease, they were not primarily focused on this subgroup of patients. Despite the significant long-term benefit, the use of BITA has not been universally adopted, mainly because it is technically more demanding, and the benefit has not been confirmed in RCTs. The Arterial Revascularization Trial (ART) was designed to answer the question if BITA was superior to SITA in multivessel disease but failed to demonstrate a significant benefit in the long-term survival. (2) It neither specified how many patients included had LMCA disease, making it difficult to extrapolate these results to clinical practice in this group of patients. (3)

The results of other RCTs focused on patients with LMCA disease also failed to demonstrate any benefit. The sub-analysis of a RCT (EXCEL trial), designed to evaluate if PCI was noninferior to CABG in LMCA disease, explored if BITA was superior to SITA in the group of patients included in the CABG surgery arm. (4) Although the study had poor statistical power to detect a significant difference because of the study design and the important statistically significant differences in the baseline characteristics (11 of 22 variables reported in Table 1), the authors concluded that there was no evidence of benefit in the composite outcome of mortality, myocardial infarction and stroke at 3-year follow-up. Thus, there is still controversy about the best surgical technique to manage LMCA disease.

Considering that CABG surgery is the standard of care (gold standard) to test new therapeutic technologies, such as implantation of new-generation stents to treat LMCA disease, and the heterogeneity of the different techniques for CABG surgery worldwide and in our country, it is extremely important to determine which is the best surgical technique in terms of long-term survival (10 years). Therefore, the aim of our study was to evaluate if BITA is associated with greater long-term survival in LMCA disease.

METHODS

We conducted a comparative observational analysis adjusted for risk, of data prospectively collected from November 1996 to May 2014 at a single center. The cohort was made up of

consecutive patients with LMCA disease and involvement of at least two coronary artery territories who underwent off-pump CABG surgery and received at least one bypass graft with at least one in situ mammary artery graft which is universally accepted as the gold standard in CABG. Off-pump surgery is the standard of care in our institution. Patients requiring emergency surgery (within 24 hours), on-pump surgeries, and patients with history of CABG surgery were excluded. Patients were stratified according to the number of internal mammary arteries used, into BITA Group (2 thoracic arteries) and SITA Group (1 thoracic artery + another conduit). The surgical technique used in both groups has already been described. (5) The primary endpoint was all-cause mortality at 10 years since it is less amenable to interpretation.

All patient data were prospectively collected in our customized database (Microsoft Access; Microsoft Corp, Redmond, WA), which is used in our daily practice. Preoperative, intraoperative, and postoperative data were obtained by retrospective review of the clinical reports in the database and cross-checked with all the medical records. The preoperative characteristics of the patients in these study groups were summarized as mean \pm standard deviation, median and interquartile range (IQR) or incidence (percentage), as appropriate. Continuous variables were compared using the Student's t test for independent samples or Mann-Whitney U test, and the chi-square test or Fisher's exact test were used to compare categorical variables.

A propensity score for having BITA grafting was calculated for each patient using a logistic regression model that included all the preoperative variables listed in Table 1. Patients were matched 1:1 by the propensity scores using the greedy matching technique without replacement. A nearest-neighbor-matching algorithm was used with a caliper distance of 0.1. Outcomes of interest between the matched groups were compared using the paired t test for continuous variables and the McNemar test for categorical variables. After matching, we examined the balance of all observed covariates, interactions among all covariates, and quadratic terms of all covariates. Preoperative differences between the groups were evaluated using standardized differences. Changes in imbalance were plotted (before and after propensity score matching). Event-free survival curves were estimated using the Kaplan-Meier method. A stratified multivariate Cox regression model was used to estimate the effect of BITA on long-term survival among the matched groups. The first block of the regression model included the type of conduit used and the second block included the operative variables using the backward stepwise likelihood ratio method to account for matching.

Univariate and multivariate Cox proportional hazard analyses were performed to investigate the significant predictors of late mortality. The variables used for univariate analysis were the clinical variables listed in Table 1. Variables with a p value $<$ 0.2 on univariate analysis were included in the multivariate model. Three statistical tests (likelihood ratio test, Wald test, and logrank test) were used to ensure the goodness of fit of the model. Global Schoenfeld test and covariate specific Schoenfeld individual test were applied to evaluate the proportional hazards assumption in the Cox proportional hazards model.

Long-term survival was evaluated by direct communication with the patient, family and treating physicians. The medical records were also reviewed.

Ethical considerations

All the patients signed an informed consent form regarding the surgical method, the postoperative evaluations and the

Table 1. Patients' characteristics

	UNADJUSTED RISK DATA			ADJUSTED RISK DATA			MSD‡
	SITA (n = 144)	BITA (n = 579)	p	SITA (n = 107)	BITA (n = 107)	p	
Age, years, m (SD)	70.0 (9.3)	65.3 (9.0)	<0.001	68.9 (9.3)	69.2 (9.7)	0.831	0.029
Female sex,	20.10%	8.80%	<0.001	24.30%	15.00%	0.121	0.137
Weight, kg, m (SD)	79.4 (19.0)	81.6 (12.9)	0.254	80.9 (20.4)	78.5 (12.5)	0.352	0.142
Height, cm, m (SD)	168.3 (8.7)	172.1 (7.3)	<0.001	168.3 (9.0)	170.5 (8.8)	0.115	0.145
Hypertension	79.20%	79.40%	0.941	78.50%	79.40%	0.867	0.023
Dyslipidemia	73.60%	79.80%	0.106	72.90%	73.80%	0.877	0.021
Family history	26.40%	27.50%	0.796	25.20%	24.30%	0.874	0.022
Diabetes mellitus	25.70%	26.60%	0.826	28.00%	25.20%	0.643	0.063
Smoking habits (current or former smoker)	54.90%	67.0%	0.009	55.1	63.6	0.266	0.172
Previous stroke	1.40%	4.50%	0.084	0.90%	3.70%	0.175	0.186
COPD	5.60%	4.50%	0.589	4.70%	2.80%	0.471	0.099
Chronic kidney disease (including dialysis requirement)	6.30%	4.30%	0.327	7.50%	5.60%	0.581	0.076
LVEF < 45%	22.90%	13.30%	0.004	18.70%	18.70%	>0.99	<0.001
History of myocardial infarction	21.50%	25.40%	0.336	21.50%	26.20%	0.422	0.110
Previous PCI	17.40%	16.90%	0.901	17.80%	21.50%	0.491	0.094
Peripheral artery disease	6.30%	3.30%	0.099	4.70%	2.80%	0.471	0.099
Lower extremities							
Carotid artery disease (only medical treatment),	4.20%	5.70%	0.466	3.70%	2.80%	0.701	0.053
Carotid artery disease (treated with surgery/ endovascular procedure),	0.00%	1.90%	0.096	0.00%	0.00%	>0.99	<0.001
Abdominal artery disease	2.80%	1.00%	0.109	1.90%	0.90%	0.561	0.080
Elective surgery	40.30%	46.60%	0.171	38.30%	46.70%	0.213	0.171
Two-vessel coronary artery disease	28.50%	31.30%	0.516	26.20%	35.50%	0.139	0.132
Three-vessel coronary artery disease	71.50%	68.70%	0.516	73.80%	64.50%	0.139	0.132
Previous cardiac surgery							
Valve replacement + CABG	1.40%	0.00%	0.005	0.00%	0.00%	>0.99	<0.001
Isolated heart valve surgery	1.40%	0.00%	0.005	0.00%	0.00%	>0.99	<0.001

SITA: single internal thoracic artery; BITA: bilateral internal thoracic artery; SDM: standardized differences in means; SD: standard deviation; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft.

use of anonymized clinical data for academic purposes. The study was approved by the institutional review board of *Instituto Cardiovascular de Buenos Aires*.

RESULTS

Of 3,757 patients undergoing elective or urgent CABG surgery due to multivessel disease, 723 met the inclusion criteria (19.2%) and were stratified according to the number of internal mammary arteries used into BITA group (2 mammary arteries, n=579, 80.1%) and SITA group (1 mammary artery + another conduit, n=144, 19.9%). The preoperative characteristics of the study population are presented in Table 1. Patients in the BITA group were younger (BITA, 65.3 ± 9.1 years versus SITA, 70.0 ± 9.9 years; p < 0.0001) and taller (p < 0.001); the history of CABG surgery was less common (p < 0.01) and fewer patients had

moderate or severe left ventricular dysfunction (p = 0.004).

After propensity score matching, 107 comparable matched sets were obtained (n=214), with no significant differences in their baseline characteristics (Table 1). The preoperative differences between the groups were evaluated using standardized differences. There were no imbalances as assessed through univariate and multivariate tests. The overall chi-square balance test (Hansen and Bowers) (6) was also not significant (chi-square [degrees of freedom: 18] = 8.474; p = 0.998). The multivariate imbalance measure (Iacus, King, and Porro, L1) was larger in the unmatched sample (0.972) than in the matched sample (0.935), also indicating that matching improved overall balance. (7)

Follow-up of hospital survivors was complete in

96.2 %: BITA group vs. SITA group, 91.8 % vs. 95.6 %, with no significant differences ($p = 0.136$). Median follow-up of all the patients was 5.2 years (IQR 2.2 - 8.1 years), with no significant difference between both groups ($p = 0.189$). Figure 1 shows the unadjusted 10-year outcomes with greater 10-year survival for the BITA group ($79.0\% \pm 3.4\%$ vs. $67.0\% \pm 4.9\%$, p log-rank test = 0.008).

In addition, in the risk-adjusted population (according to propensity score) BITA patients had significantly higher survival than SITA patients at the end of follow-up, $93.0\% \pm 4.6$ vs. $69.0\% \pm 5.7$ respectively (HR: 0.27, 95%CI: 0.07-0.76, $p = 0.016$, univariate Cox model). BITA grafting was also a predictor of better survival on multivariate analysis (HR 0.26, 95% CI, 0.08-0.89, $p = 0.03$, Cox multivariate model).

Time-to-event analysis using multivariate Cox regression identified better 10-year survival in the BITA group (HR 0.57, 95% CI, 0.37-0.87, $p < 0.01$) (Table 2). Long-term survival was significantly higher in the BITA group vs. the SITA group. The Schoenfeld test was not statistically significant for each of the covariates, and the global test was also not statistically significant ($p = 0.6595$). Therefore, we can assume the proportional hazards of the Cox model.

DISCUSSION

The use of both internal thoracic arteries with an off-pump technique seems to improve long-term survival of patients with LMCA disease compared with a more traditional revascularization surgery using a single internal thoracic artery plus another conduit (radial artery graft or saphenous vein graft).

There is significant discrepancy between large risk-adjusted observational trials and RCTs regarding both surgical techniques. Four RCTs comparing BITA

and SITA in multivessel disease reported no differences in mid-term survival at 5 years. (8-11) None of these studies mentioned LMCA disease in their design, (3) so it would not be reasonable to extrapolate their conclusions to LMCA disease. In addition, mid-term follow-up could be insufficient to show better survival with the use of the arterial conduit. Other important methodological issues, as on-pump or off-pump interventions, could have also modified the treatment effect. The surgical techniques were not standardized or homogeneous, so that the surgeon could perform on-pump or off-pump procedures, which is still a major issue of controversy for long-term survival. (12-14) Of these RCTs, the ART trial was not only the largest trial but also had the longest follow-up (10 years). Unfortunately, there are other methodological concerns about this trial. Although the primary analysis used the intention-to-treat principle, crossover between groups was $> 36\%$; therefore, only 64% of the randomized patients received the assigned treatment and only 40.9% (1259 patients out of 3078) were off-pump procedures. (15) Considering these limitations, we designed the present study including only off-pump operations to standardize the surgical technique and because it is the standard of care in our institution.

On the other hand, evidence from large observational studies supported the use of both mammary arteries in multivessel disease, as demonstrated in 6 meta-analyses. (16-21) The largest meta-analysis included 29 observational studies, with a total of 89 399 patients. Pooled data yielded a significantly higher long-term survival (10 years) for the BITA group compared with that of the SITA group (82.1% vs. 70.5% , HR 0.78; $p < 0.00001$). In the present study, performed exclusively in patients with LMCA disease, we observed a similar benefit.

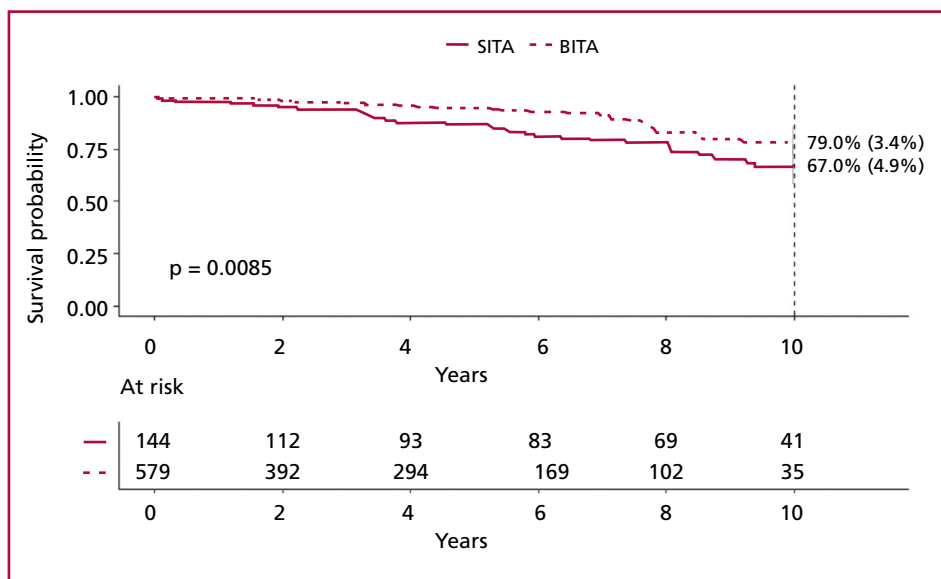


Fig. 1. Unadjusted long-term all-cause mortality. BITA: bilateral internal thoracic artery; SITA: single internal thoracic artery.

Fig. 2. Risk-adjusted long-term all-cause mortality (propensity score matching). BITA: bilateral internal thoracic artery; SITA: single internal thoracic artery.

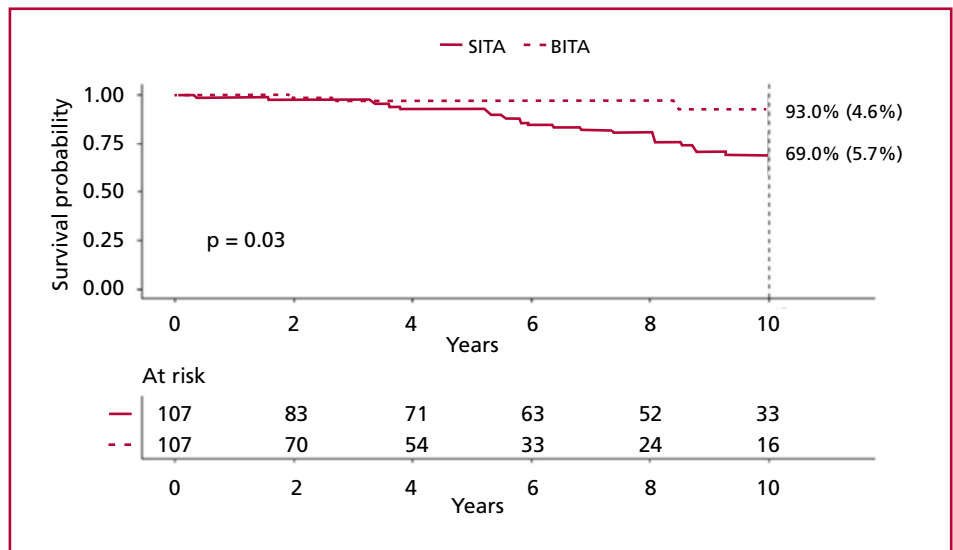


Table 2. Multivariate Cox proportional hazard regression for all-cause mortality at 10 years

	HR	95% CI	p
Peripheral artery disease	2.06	1.07 - 3.99	0.032
Chronic kidney disease (including dialysis requirement)	3.06	1.55 - 6.03	0.001
Elective surgery	0.56	0.36 - 0.87	0.010
Postoperative myocardial infarction	3.43	1.32 - 8.87	0.011
BITA	0.57	0.37 - 0.87	0.010

BITA: bilateral internal thoracic artery

The evidence about the best surgical strategy for managing LMCA disease is still limited. One could argue that it is not so different from multivessel disease. Although this may be true from the surgeon's point of view, it is very different for interventional cardiologists. Surgery treats the vessel affected by atherosclerosis, whereas percutaneous coronary intervention treats each lesion of the vessel. In this regard, some RCTs compared new technologies used in PCIs with CABG surgery, including any surgical strategy. These methodological designs imply accepting that all surgical techniques provide the same benefits. But is it really true? In the present study, we observed a significant difference in favor of BITA versus SITA in 10-year all-cause mortality, providing further evidence that not all CABG surgeries offer the same benefits. A sub-analysis of the EXCEL trial addressed this issue by analyzing only the surgical arm. Among the 905 patients undergoing CABG, 688 (76.0%) underwent SITA and 217 (24.0%) underwent BITA. There were no significant differences in 3-year survival (HR 1.36; 95% CI, 0.60-3.12; $p = 0.46$). Probably this short follow-up was insufficient to demonstrate the benefit of the second arterial conduit. In fact, in the present study the probability of survival at 3-year follow-up was not significantly different between the two groups ($97.0\% \pm 0.8\%$ vs. $94.0\% \pm 2.1\%$, $p = 0.1$); with significant differences at 10 years ($79.0\% \pm 3.4\%$ vs. $67.0\% \pm 4.9\%$, $p = 0.008$).

This study has several limitations. The main limitation is its design, a retrospective observational comparative study conducted in a single center. To mitigate the confounding effect, two different and independent statistical methods were used (propensity score matching and multivariate Cox regression). In addition, we only included patients who underwent off-pump CABG surgery to reduce the possible effect of on-pump or off-pump on the outcome. However, although every effort was made to minimize the effect of confounders, we cannot rule out the effect of those unmeasured. (21)

In conclusion, this study suggests that coronary artery bypass graft surgery for LMCA disease exclusively with BITA as composite T-graft and off-pump technique can be safely performed and could be associated with improved long-term survival compared with the more traditional strategy using a mammary artery graft plus another conduit.

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