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Long-term survival of single versus bilateral internal mammary artery grafting in patients under 70

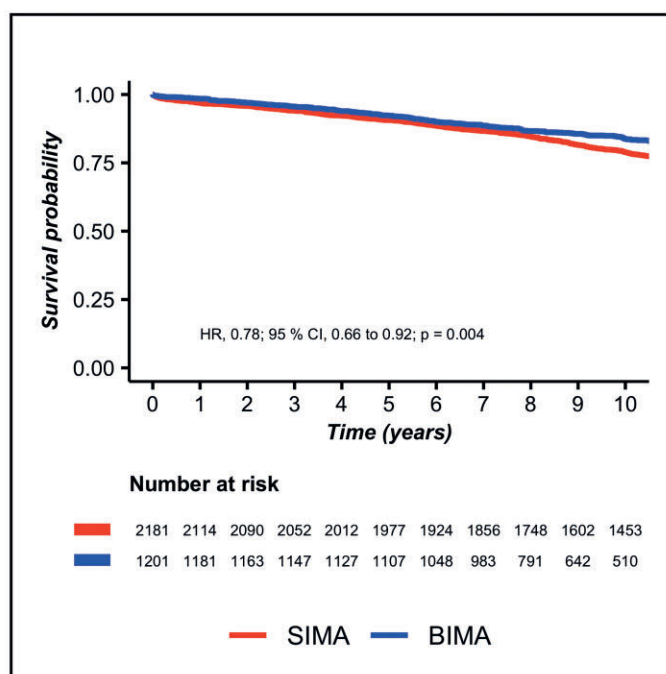
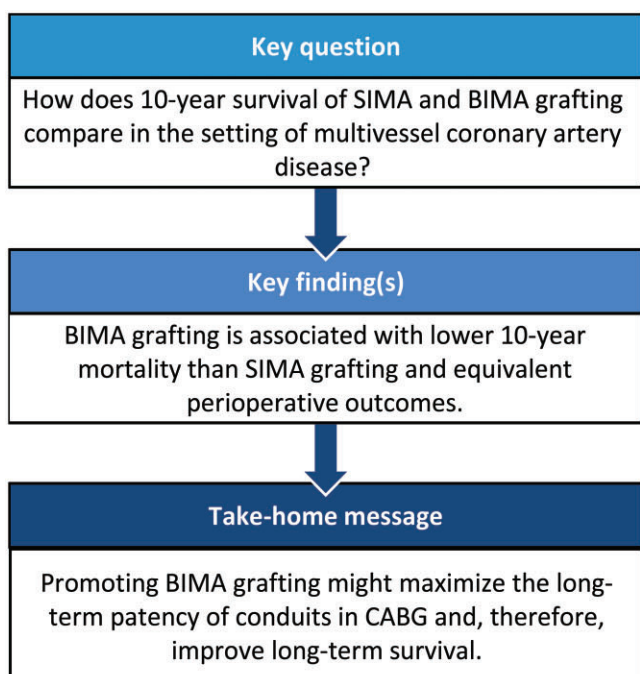
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Abstract

OBJECTIVES: As definitive data from randomized controlled trials comparing the effect on long-term survival of using single internal mammary artery (SIMA) or bilateral internal mammary artery (BIMA) grafting are not yet available, observational studies allow for long-term follow-up in large and representative populations, which might complement the information potentially derived from randomized trials. To compare long-term survival in patients under 70 years of age undergoing SIMA or BIMA grafting.

METHODS: Retrospective analysis of 3384 consecutive patients under 70 years undergoing primary isolated coronary artery bypass grafting, performed from 2000 to 2015, in a Portuguese level III Hospital. We identified 2176 and 1208 patients from the study population who underwent SIMA and BIMA grafting, respectively. The primary end point was all-cause mortality at 10 years. We employed inverse probability weighting to restrict confounding by indication.

RESULTS: The mean age of the study population was 59.4 (\pm 7.6) years, and 567 (16.8%) were females. Inverse probability weighting was effective in eliminating differences in all significant baseline characteristics. Follow-up was 99.88% complete. The median follow-up time was 12.82 (interquartile range, 9.65, 16.74) years: the primary end point of all-cause mortality at 10 years occurred in 463 patients (21.3%) and 166 (13.7%) in the SIMA and BIMA grafting groups, respectively (hazard ratio, 0.78; 95% confidence interval, 0.66–0.92; P = 0.004).

CONCLUSIONS: Bilateral internal mammary grafting is associated with lower long-term mortality than single internal mammary grafting. Moreover, this survival benefit comes at no increased perioperative morbidity or mortality cost.

Keywords: Coronary artery bypass grafting • Internal mammary coronary artery anastomosis • Propensity score • Survival analysis

ABBREVIATIONS

BIMA	Bilateral internal mammary artery
CABG	Coronary artery bypass grafting
CI	Confidence interval
GDMT	Guideline-directed medical therapy
ICD-9-CM	International classification of diseases, 9th edition, clinical modification
IMA	Internal mammary artery
IPW	Inverse probability weighting
IQR	Interquartile range
OR	Odds ratio
SIMA	Single internal mammary artery
SMD	Standardized mean difference
SVGs	Saphenous vein grafts

INTRODUCTION

As outcomes following coronary artery bypass grafting (CABG) are ultimately related to long-term graft patency, the choice of bypass conduits plays a central role in this surgical procedure [1]. The internal mammary artery (IMA) possesses exceptional biological properties that confer relative resistance to atherosclerosis and better long-term patency than saphenous vein grafts (SVGs), making it a conduit of choice for CABG [2–4]. Therefore, Loop *et al.* [5] established the use of the left IMA to the left anterior descending artery as the standard of care and demonstrated that it prolonged survival and improved long-term results after CABG. Consequently, it seems intuitive that if a single IMA (SIMA) was good, bilateral IMAs (BIMA) would be better [6].

Lytle *et al.* [7] from the Cleveland Clinic published the first comprehensive analysis of clinical results of BIMA grafting. Since their publication, several meta-analyses of single-institution observational studies have confirmed that BIMA grafting is associated with significantly reducing long-term mortality [8–13]. Yet, even though they provide important information when prospective randomized trials are unavailable, they remain limited by their potential for selection bias. However, the Arterial Revascularization Trial, designed to answer whether BIMA can improve 10-year survival compared with SIMA, failed to demonstrate a significant between-group difference in the death rate from any cause at 10 years [14], despite its intensely debated methodological limitations [15, 16].

This article aims to compare long-term survival in patients under 70 years of age undergoing SIMA versus BIMA in a large single-centre inverse probability-weighted (IPW) cohort of patients. IPW creates a pseudo-population of the treatment and the control group, with the same covariate distribution as the overall treated and untreated population [17]. This methodology allows us to estimate the average treatment effect in the entire population, the same question asked in a randomized controlled trial.

MATERIALS AND METHODS

Ethical statement

The São João University Hospital Center Ethics Committee approved this research and waived the need for informed consent.

Study design

We conducted an observational retrospective study to evaluate SIMA and BIMA utilization trends, in-hospital complications, length of hospital stay, discharge disposition and long-term (10 years) survival in patients with isolated coronary artery disease undergoing CABG. Thus, we analysed an administrative dataset containing all hospitalizations occurring in a tertiary care hospital from 1 January 2000 to 30 September 2015 [chosen as the cut-off date because of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-10-CM) implementation]. The corresponding diagnoses and procedures were coded for each hospitalization based on the ICD-9-CM.

Study population

Patients were included in the study if they were under the age of 70 years and underwent primary CABG (ICD-9-CM codes 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17 or 36.19) during the study period, with >1 graft performed. Exclusion criteria included previous cardiac surgery, concomitant valve replacement or repair, concurrent aorta surgery and simultaneous correction of myocardial infarction mechanical complications (Supplementary Material, Table S1).

Data sources and variables

From an administrative dataset containing all hospitalizations occurring in our Institution from 2000 to 2015, we identified all hospitalizations with at least 1 associated procedure code of CABG. The predictive or independent variable was the treatment modality of CABG, a dichotomous variable defined by the presence of ICD-9-CM code 36.16 (BIMA, the intervention) or 35.15 (SIMA, the comparator). We obtained patients' baseline characteristics from our institution patient's discharge datasets. After extracting the relevant ICD-9-CM codes, we computed the Charlson Comorbidity Index using the Quan *et al.* coding scheme [18]. We provide definitions of coexisting conditions in Supplementary Material, Table S2.

Outcomes

We compared episodes coded as BIMA grafting to those coded as SIMA grafting. The primary outcome variable was 10-year survival. The patient discharge database was linked to the Portuguese National Patient Registry to ascertain patient life status. Secondary outcomes included a set of predefined in-hospital

complications (see [Supplementary Material, Table S3](#) for detailed definitions), the length of hospital stay and discharge disposition (categorized as home discharge, transfer to other healthcare facilities or in-hospital death).

Statistical analysis

Data are presented as absolute frequencies and percentages for categorical variables and as means and standard deviations for continuous variables. We used the standardized mean difference (SMD) to assess discrepancies in covariates between treatment groups, as it allows for the judgement of the relative balance of variables measured in different units. We held values <0.1 to indicate a negligible difference in the mean or frequency of a covariate between treatment groups.

In the univariable analysis, we computed summary measures of risk [odds ratio (OR)], its associated 95% confidence interval (CI) and a chi-squared test for difference in the observed proportions from count data presented in a two-by-two table for each of the predefined outcomes.

We employed IPW to restrict confounding by indication. IPW makes sense with an active comparator, allowing us to estimate the average treatment effect in the entire population. Making these causal contrasts depends on predicting treatment based on relevant covariates, that is the propensity score estimation. Multivariable logistic regression was used in each treatment group to estimate each patient's probability of undergoing BIMA grafting (i.e. the propensity score). The propensity model

included the following variables: sex, age, admission status (scheduled vs unscheduled), disease presentation (stable coronary disease, unstable angina/non-ST-elevation myocardial infarction and ST-elevation myocardial infarction), hypertension, diabetes mellitus, hyperlipidaemia, obesity, smoking history, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, chronic kidney disease, liver disease, anaemia, coagulation disorders, cancer history and the Charlson comorbidity index. We calculated stabilized weights by dividing the marginal probability of the observed treatment by the propensity score for the treatment received. Finally, we assessed the balance between treatment groups using SMDs, with an ideal balance represented by a standardized difference of 10% or less. We included visual depictions of distributional balance as they are a helpful complement to numerical summaries.

We derived weighted logistic regression models with a robust variance estimator with the outcome as the dependent variable and the group on which the propensity score balances (e.g. the treatment group) as the only independent/predictor variable.

Estimates of survival probabilities were calculated using the Kaplan-Meier method and compared with the log-rank test. Follow-up time, described by median and interquartile range (IQR), was obtained using the same estimator by reversing the event indicator so that the outcome of interest became being censored. We employed a weighted Cox proportional hazards regression model with a robust variance estimator to compare long-term mortality between groups.

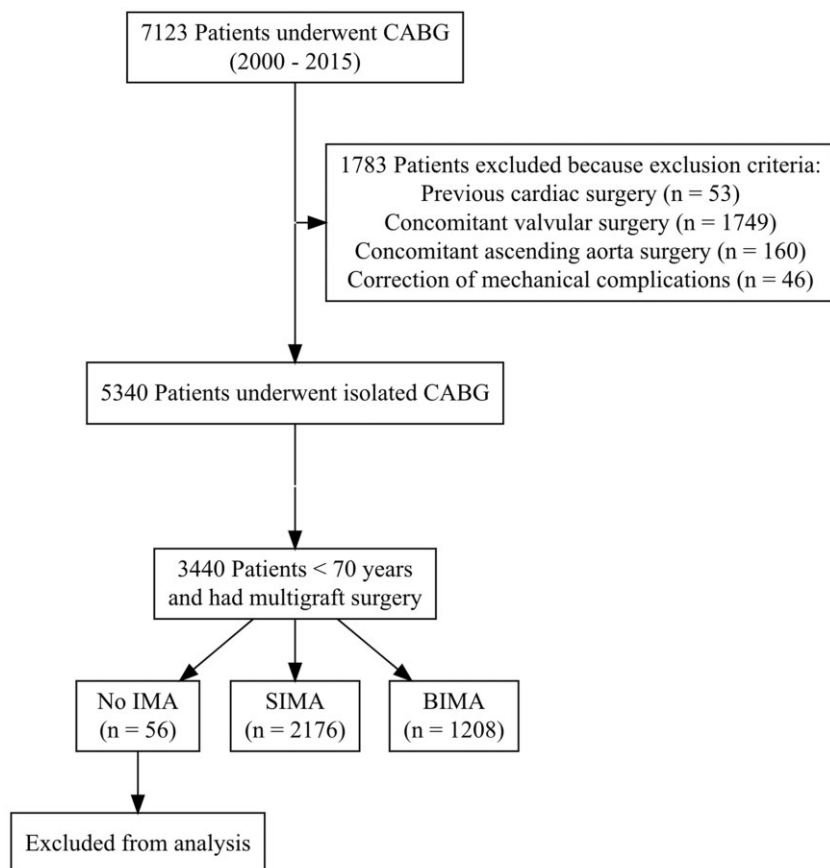


Figure 1: Study flowchart.

P-values <0.05 were considered statistically significant. All statistical analyses were performed using R, version 4.1.2 [19].

RESULTS

Of 7123 patients who underwent CABG during the study period, 3440 were eligible for inclusion in the study (Fig. 1): 2176 patients in the SIMA group (63.3%) and 1208 patients in the BIMA group (35.1%). In this time frame, 3384 (98.4%) received at least 1 IMA graft. The mean age of the study population was 59.4 (\pm 7.6) years, and 567 (16.8%) were females. Figure 2 portrays the annual trend of relative BIMA and SIMA utilization during the study period. In this time frame, BIMA utilization was \sim 0.5% in 2000, and it rose to \sim 80% in 2015 in this patient population.

Baseline characteristics

Patients in the BIMA group were less likely to be female (13.2% vs 18.7%, SMD 0.149), were younger (56.82 ± 7.65 vs 60.76 ± 7.24 years, SMD 0.529) and were more likely to be operated on following an acute coronary syndrome (40.2% vs 34.2%, SMD = 0.165), less likely to have diabetes mellitus (35.5% vs 40.0%, SMD 0.152) and more likely to have a past or current

smoking history (53.9% vs 40.6%, SMD = 0.274). In addition, BIMA patients presented with lower Charlson comorbidity index scores (3.49 ± 1.44 vs 3.81 ± 1.38 , SMD = 0.224). IPW effectively eliminated differences in all baseline characteristics (Table 1 and Fig. 3), as revealed by SMD values below 0.10. The mean stabilized weight was close to 1, and its maximum value was inferior to 10 (actually, 5.67), so no trimming procedure was necessary as a sensitivity analysis.

Unadjusted analysis

In the crude univariable analysis (Table 2), BIMA patients were less likely to require longer mechanical ventilation times (2.3% vs 4.5%, OR = 0.50, 95% CI 0.32–0.75, $P < 0.001$) and to demand orotracheal reintubation less often (1.4% vs 2.4%, OR = 0.58, 95% CI 0.33–0.99, $P = 0.055$). Regarding discharge disposition, BIMA patients were more likely to go directly home after the index hospitalization (96.9% vs 95.3%, OR = 1.56, 95% CI 1.07–2.31, $P = 0.023$). We have not noted any other differences in the rates of pre-specified complications. Concerning the length of hospital stay (Table 2), BIMA patients required shorter median hospitalization periods: change in the estimate of -1.6 days (95% CI -2.2 to -1.1, $P < 0.001$).

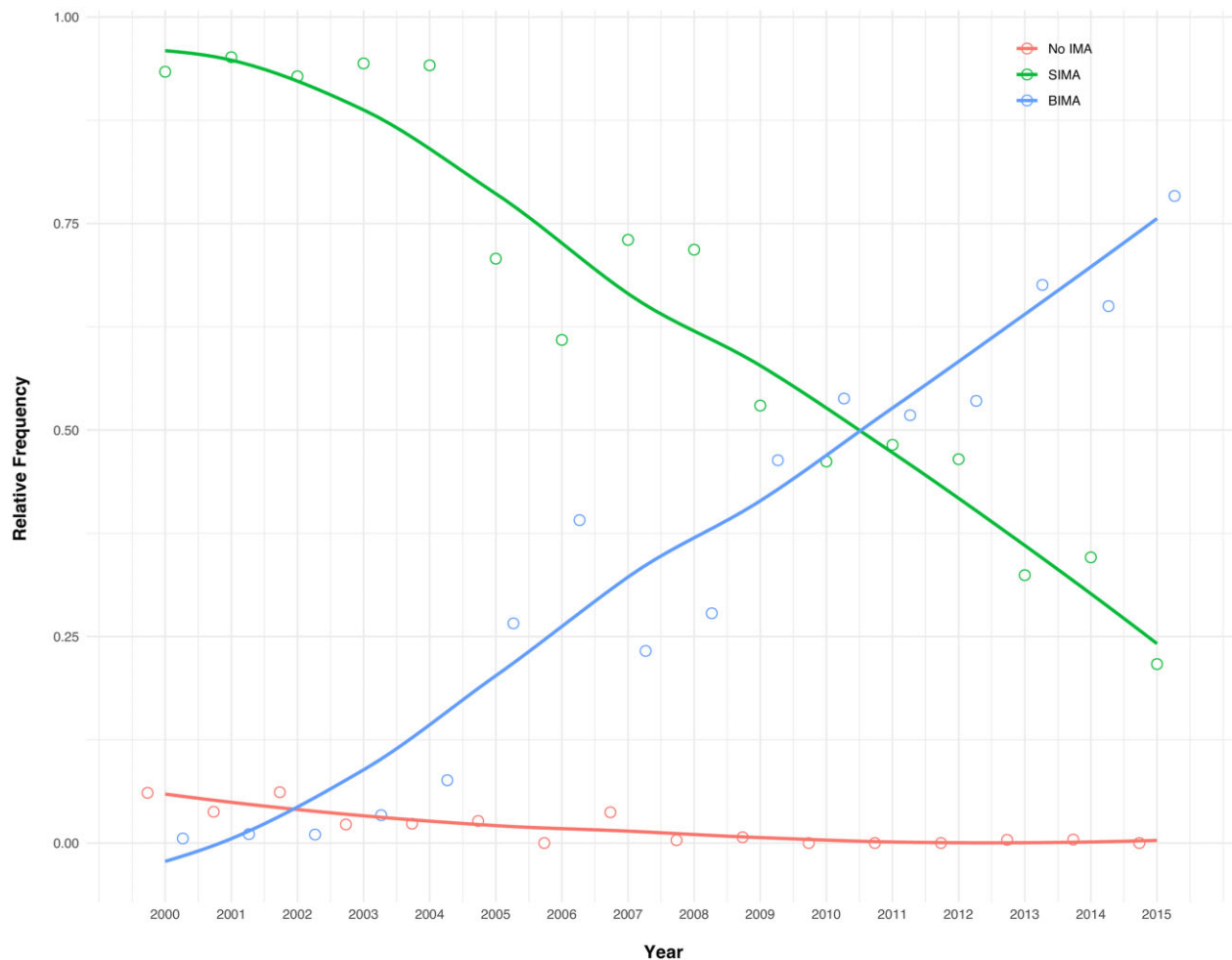


Figure 2: Temporal trends in single internal mammary artery versus bilateral internal mammary artery grafting (2000–2015).

Table 1: Baseline characteristics for unweighted and inverse probability weighting cohorts: single internal mammary artery versus bilateral internal mammary artery

Characteristic	Unadjusted cohort			IPW cohort		
	SIMA (n = 2176)	BIMA (n = 1208)	SMD	SIMA (n = 2184.8)	BIMA (n = 1200.8)	SMD
Female, n (%)	407 (18.7)	160 (13.2)	0.149	367.1 (16.8)	203.8 (17.0)	0.004
Age, mean (SD)	60.76 (7.24)	56.82 (7.65)	0.529	59.20 (8.09)	59.16 (7.23)	0.005
Admission, n (%)			0.040			0.012
Scheduled	1040 (47.2)	553 (45.8)		1024.9 (47.3)	574.6 (47.9)	
Unscheduled	1136 (52.2)	655 (54.2)		1151.9 (52.7)	626.2 (52.1)	
Presentation, n (%)			0.165			0.006
Chronic CAD	1432 (65.8)	722 (59.8)		1394.3 (63.8)	769.3 (64.1)	
UA/NSTEMI	520 (23.9)	377 (31.2)		578.8 (26.5)	314.8 (26.2)	
STEMI	224 (10.3)	109 (9.0)		211.6 (9.7)	116.8 (9.7)	
Hypertension, n (%)	1424 (65.4)	777 (64.3)	0.023	1410.4 (64.6)	772.9 (64.4)	0.004
Diabetes mellitus, n (%)			0.152			0.005
No diabetes	1305 (60.0)	779 (64.5)		1349.7 (61.8)	742.8 (61.9)	
Non-insulin treated	771 (35.4)	350 (29.0)		717.6 (32.8)	394.7 (32.9)	
Insulin treated	100 (4.6)	79 (6.5)		117.5 (5.4)	63.3 (5.3)	
Hyperlipidaemia, n (%)	1392 (64.0)	832 (68.9)	0.104	1437.8 (65.8)	791.6 (65.9)	0.002
Obesity, n (%)	517 (23.8)	330 (27.3)	0.082	544.3 (24.9)	297.5 (24.8)	0.003
Smoking history, n (%)			0.274			0.009
No smoking history	1292 (59.4)	557 (46.1)		1190.5 (54.5)	659.8 (54.9)	
Previous smoker	460 (21.1)	312 (25.8)		494.2 (22.6)	269.2 (22.4)	
Current smoker	424 (19.5)	339 (28.1)		500.1 (22.9)	271.9 (22.6)	
CVD, n (%)	286 (13.1)	176 (14.6)	0.041	292.2 (13.4)	159.6 (13.3)	0.002
CHF, n (%)	401 (18.4)	197 (16.3)	0.056	381.5 (17.5)	202.6 (16.9)	0.016
COPD, n (%)	129 (5.9)	92 (7.6)	0.067	140.3 (6.4)	77.3 (6.4)	0.0005
PVD, n (%)	65 (3.0)	57 (4.7)	0.090	78.0 (3.6)	43.2 (3.6)	0.002
CKD, n (%)			0.031			0.002
No chronic kidney disease	2082 (95.7)	1154 (95.5)		2091 (95.7)	1150 (95.7)	
Non-dialysis dependent	79 (3.6)	48 (4.0)		80.8 (3.7)	44.1 (3.7)	
Dialysis dependent	15 (0.7)	6 (0.5)		13.2 (0.6)	7.2 (0.6)	
Liver disease, n (%)	47 (2.2)	22 (1.8)	0.024	44.2 (2.0)	23.9 (2.0)	0.003
Anaemia, n (%)	198 (9.1)	77 (6.4)	0.102	180.3 (8.3)	103.1 (8.6)	0.012
Coagulation disorders, n (%)	34 (1.6)	11 (0.9)	0.059	27.8 (1.3)	12.2 (1.0)	0.024
Cancer, n (%)	15 (0.7)	8 (0.7)	0.003	14.7 (0.7)	8.4 (0.7)	0.003
CCI, mean (SD)	3.81 (1.38)	3.49 (1.44)	0.224	3.67 (1.43)	3.66 (1.37)	0.008

BIMA: bilateral internal mammary artery; CAD: coronary artery disease; CCI: Charlson comorbidity index; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; IPW: inverse probability weighting; PVD: peripheral vascular disease; SD: standard deviation; SIMA: single internal mammary artery; SMD: standardized mean difference; STEMI: ST-elevation myocardial infarction; UA/NSTEMI: unstable angina/non-ST-elevation myocardial infarction.

Weighted analysis

IPW resulted in balanced baseline characteristics in each group (Fig. 3). As depicted in Fig. 4, BIMA patients were less likely to require longer mechanical ventilation times (2.4% vs 4.7%, OR = 0.50, 95% CI 0.32–0.79, $P = 0.003$). We have not noted any other differences in pre-specified complications or discharge disposition rates. Concerning the length of hospital stay, there were no significant differences between groups (change in estimate 0.04 days, 95% CI -0.74 to 0.77, $P = 0.911$).

Survival analysis

Follow-up was 99.88% complete (4 patients with vital status impossible to ascertain). The median follow-up time was 12.82 (IQR, 9.65–16.74) years: 14.93 (IQR, 11.67–18.55) years for the SIMA group and 10.18 (IQR, 8.16–12.56) years for the BIMA group. The primary end point of all-cause mortality at 10 years occurred in 463 patients (21.3%) in the SIMA group, as compared with 166 (13.7%) in the BIMA group (hazard ratio, 0.78; 95% CI, 0.66–0.92; $P = 0.004$). Thirty-day and 1-, 5- and 10-year survival

rates were 99.0%, 96.9%, 90.2% and 78.0% in the SIMA group and 99.5%, 98.4%, 92.7% and 84.8% in the BIMA group. Figure 5 depicts the unweighted survival function plot for both groups. Figure 6 illustrates the weighted survival function plot for both groups. Both reveal the difference in long-term survival between groups.

DISCUSSION

In this longitudinal, population-level analysis of patients undergoing isolated primary CABG, we demonstrated that the use of BIMA for treating multivessel coronary artery disease is associated with lower long-term mortality than SIMA. Moreover, we proved that this survival benefit comes at no increased perioperative morbidity or mortality cost.

A possible explanation for our results might be that the IMA holds exceptional biological properties that grant protection to atherosclerotic plaque formation and its subsequent evolution, thus making it a conduit of choice for CABG [4]. Angiographic studies specifically directed at evaluating right IMA patency rates reported 10-year patency rates over 90%, equivalent to the left

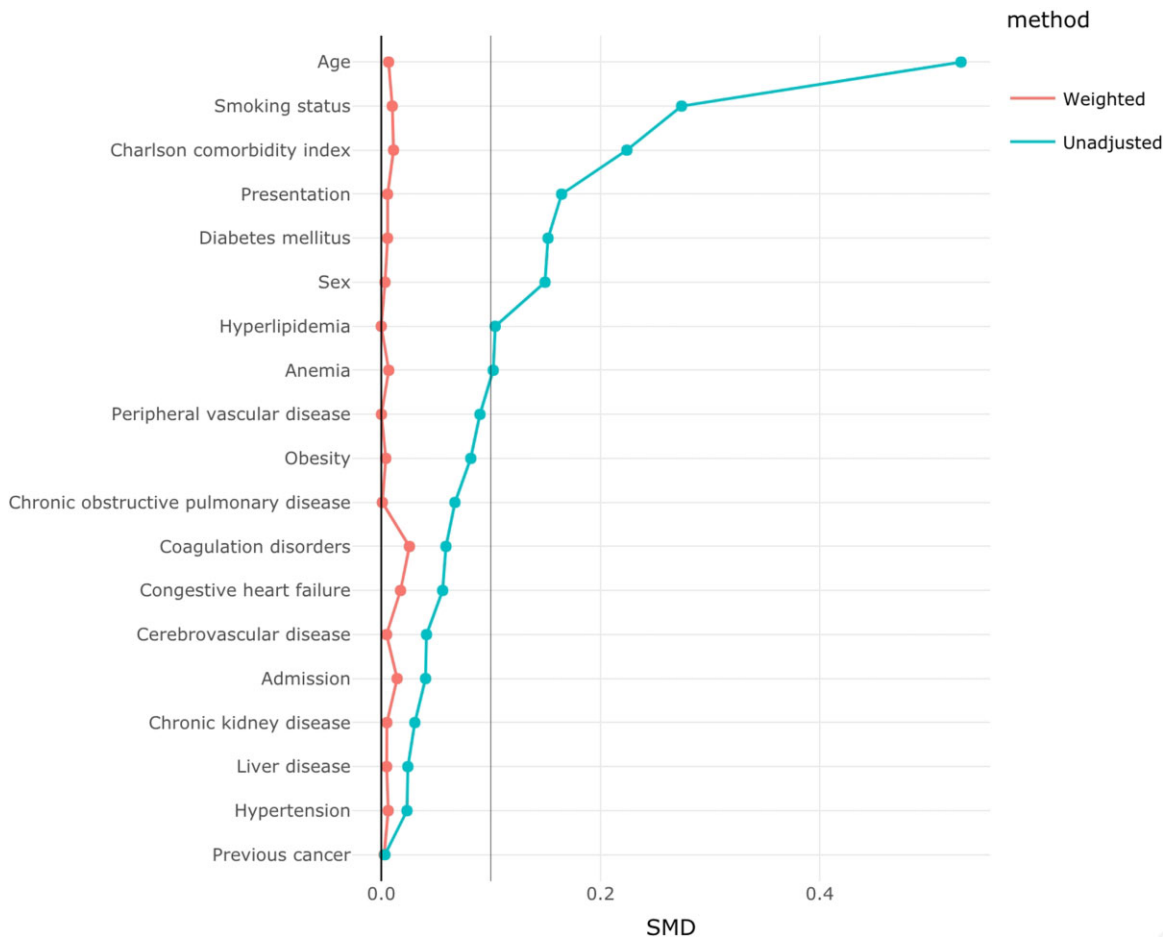


Figure 3: Covariate balance assessment.

Table 2: Crude intra- and postoperative outcomes: single internal mammary artery versus bilateral internal mammary artery

Outcome	SIMA (n = 2186)	BIMA (n = 1208)	OR (95% CI)	P-Value
Stroke, n (%)	19 (0.9)	11 (0.9)	1.04 (0.48, 2.16)	0.911
Cardiac, n (%)				
POAF	225 (10.3)	105 (8.7)	0.83 (0.65, 1.05)	0.122
Pacemaker implantation	9 (0.4)	3 (0.2)	0.60 (0.13, 2.01)	0.443
IABP	63 (2.9)	32 (2.6)	0.91 (0.59, 1.39)	0.678
Cardiac arrest	6 (0.3)	2 (0.2)	0.60 (0.09, 2.61)	0.532
Respiratory, n (%)				
Prolonged ventilation	99 (4.5)	28 (2.3)	0.50 (0.32, 0.75)	0.001
Reintubation	52 (2.4)	17 (1.4)	0.58 (0.33, 0.99)	0.055
Tracheotomy	9 (0.4)	2 (0.2)	0.40 (0.06, 1.55)	0.241
AKI, n (%)	20 (0.9)	5 (0.4)	0.44 (0.15, 1.11)	0.109
Hemorrhage, n (%)	77 (3.5)	34 (2.8)	0.79 (0.52, 1.18)	0.258
RBC transfusion, n (%)	539 (24.8)	326 (27.0)	1.12 (0.96, 1.32)	0.157
Surgical wound, n (%)	32 (1.5)	15 (1.2)	0.84 (0.44, 1.53)	0.586
Discharge disposition, n (%)				0.070
Home	2074 (95.3)	1171 (96.9)	1.56 (1.07, 2.31)	
Other hospitals	77 (3.5)	29 (2.4)	0.67 (0.43, 1.02)	
Death	25 (1.1)	8 (0.7)	0.57 (0.24, 1.22)	
LOS, median (IQR)	7 (6, 9)	6 (5, 8)	-1.6 (-2.2, -1.1)	<0.001

AKI: acute kidney injury; BIMA: bilateral internal mammary artery; CI: confidence interval; CIE: change in estimate; IABP: intra-aortic balloon pump counterpulsation; IQR: interquartile range; OR: odds ratio; POAF: postoperative atrial fibrillation; RBC: red blood cell; SIMA: single internal mammary artery; LOS: length of stay.

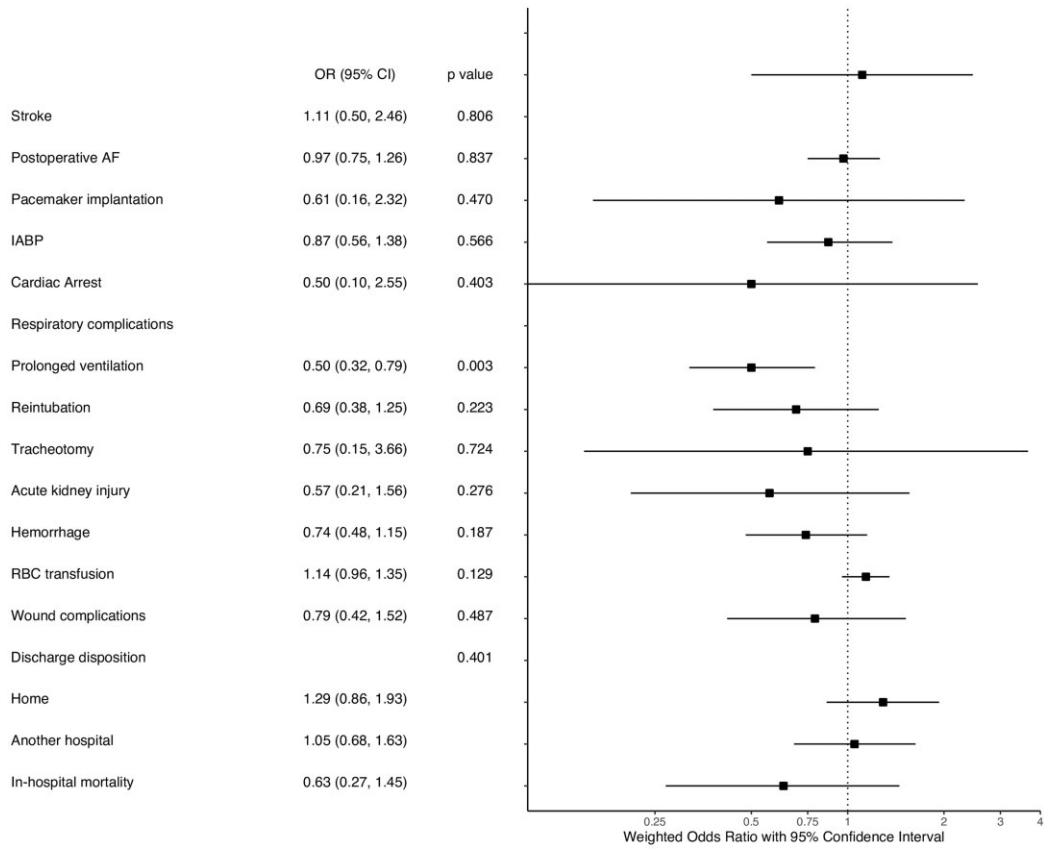


Figure 4: Weighted clinical outcomes: single internal mammary artery versus bilateral internal mammary artery.

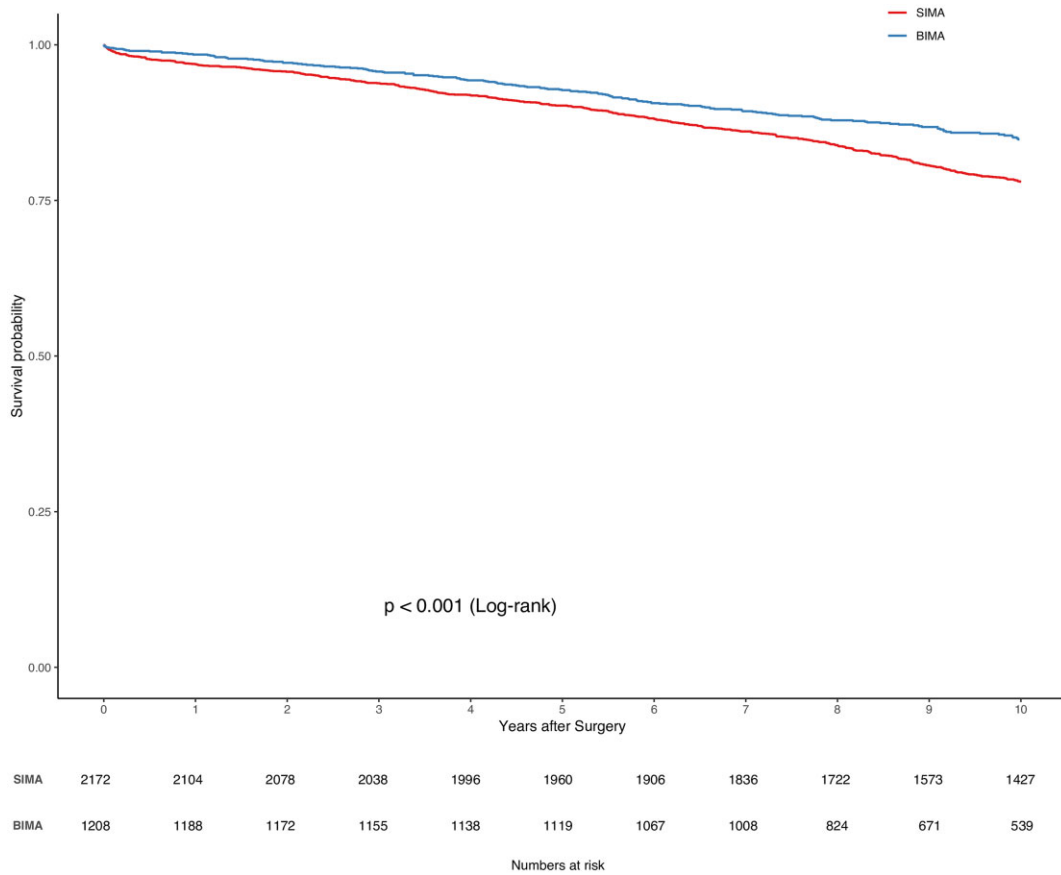


Figure 5: Long-term survival in unweighted cohort (Kaplan-Meier method): single internal mammary artery versus bilateral internal mammary artery.

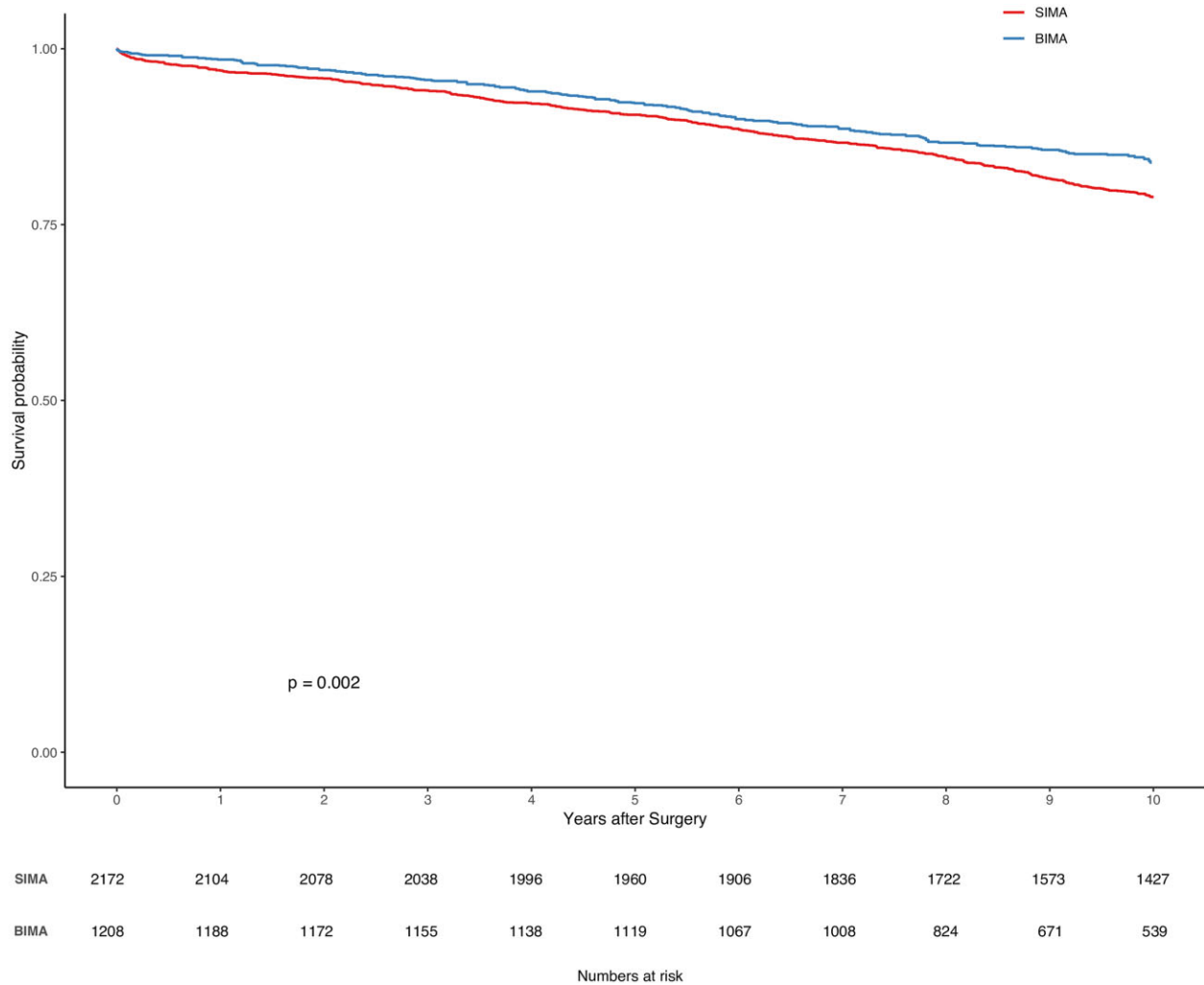


Figure 6: Long-term survival in inverse probability weighting cohort: single internal mammary artery versus bilateral internal mammary artery.

IMA for identical territories, always better than radial artery and SVG, and remain free of atheroma [20]. On the other hand, SVG durability is suboptimal, with reported 10-year patency rates of around 50%, and among these patent conduits, only 50% are free from atherosclerotic disease [21, 22]. As the long-term success of coronary revascularization depends on graft patency [23], it does make sense that BIMA grafting would fare better than SIMA supplemented by SVG.

Consistent with the aggregated findings of other observational studies in the literature [8–13], we demonstrate that BIMA grafting improved long-term survival. With a median follow-up time of over twelve years, patients receiving BIMA grafting had a 22% reduction in all-cause mortality, a survival benefit that becomes more pronounced 7 years after the procedure. One possible explanation for this finding could be the known SVGs attrition rate, which increases to ~5% per year beyond the seventh postoperative year [21].

As to randomized controlled trial-derived information, in the Arterial Revascularization Trial, among patients scheduled for CABG and randomly assigned to undergo bilateral or SIMA grafting, there was no significant between-group difference in the rate of death from any cause at 10 years in the intention-to-treat analysis [14]. Several proposed justifications could explain the neutral effect of BIMA grafting in this trial [15, 16, 24]. First, the

sample size calculations predate guideline-directed medical therapy (GDMT), such that the sample size might be too small to demonstrate a significant decrease in the proposed end-points. Second, there was a high crossover rate (14% of patients assigned to the BIMA group had an SIMA) that might be related to surgeon inexperience. Third, ~22% of SIMA patients also received a radial artery graft, which appears to have superior patency rates than SVGs, resulting in improved long-term outcomes [25]. Finally, adherence to GDMT was extremely high in this trial, and noncompliance with GDMT after CABG seems to decrease long-term survival, freedom from myocardial infarctions and the need for repeat coronary revascularization procedures [26].

Limitations

There are several limitations in our study. First, although using administrative databases allows for the efficient assessment of large populations over long periods of time, coding practices were developed for reimbursement issues, not for clinical outcome profiling. As such, imprecise or equivocal definitions may compromise coding accuracy. In addition, surgical risk models are usually based on a limited number of crucial clinical variables that typically are unavailable in administrative databases [27].

Second, we employed IPW to restrict confounding by indication, which makes sense with an active comparator, allowing us to estimate the average treatment effect in the entire study population. Nevertheless, propensity score-based methodologies do not consider factors that are not analysed, such as patients' frailty, quality of coronary artery targets, quality of venous and arterial conduits or secondary prevention after CABG. Only a prospective randomized trial, where the distribution of known and unknown confounders would be similar in both the intervention and control groups, could address these issues.

Third, although demonstrating an adjusted survival benefit of BIMA grafting is essential, we present no data on the risk of future revascularization procedures, which could lend additional support for greater BIMA use [28].

Our results have significant implications for clinical practice, as promoting BIMA grafting might maximize the long-term patency of CABG conduits and improve long-term survival. Overall, the current use of BIMA grafting in clinical practice remains relatively low, with fewer than 5% of patients in the USA and fewer than 10% in Europe receiving it [29]. The absence of randomized controlled trial-derived data to support its widespread use might explain this finding. In our cohort of patients under 70 years, BIMA grafting use was around 4% in 2000 and rose to 75% by 2015. Behind this growth is a firm conviction in the benefits of arterial revascularization among the surgical staff. In addition, we believe that the choice of revascularization strategy should be tailored to the patient and not dictated by the surgeon's ineptitude. Therefore, removing unjustified operating room time restrictions to BIMA takedown allows for proficiency in IMA harvesting, a paramount detail during training. In our experience, routinely skeletonized arteries by experienced surgeons afford little increased operative time and do not appear to increase sternal wound complications [30], even in diabetic patients.

CONCLUSION

In this longitudinal, population-level analysis of patients under 70 years undergoing primary, isolated CABG, we demonstrated that BIMA for treating multivessel coronary artery disease is associated with lower long-term mortality than SIMA. Moreover, we proved that this survival benefit comes at no increased perioperative morbidity or mortality cost.

SUPPLEMENTARY MATERIAL

[Supplementary material](#) is available at *ICVTS* online.

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Conflict of interest: none declared.

Data availability

The article's data will be shared on reasonable request to the corresponding author.

Author contributions

Armando Abreu: Conceptualization; Data curation; Formal analysis; Methodology; Software; Visualization; Writing—original draft. **José Máximo:** Writing—review & editing. **Adelino Leite-Moreira:** Writing—review & editing.

Reviewer information

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