Routine use of bilateral internal thoracic artery grafting in women: A risk factor analysis for poor outcomes☆,☆☆

Giuseppe Gatti *, Luca Maschietto, Marco Morosin, Marco Russo, Bernardo Benussi, Gabriella Forti, Lorella Dreas, Gianfranco Sinagra, Aniello Pappalardo

CardioVascular Department, Ospedali Riuniti and University of Trieste, Trieste, Italy

ARTICLE INFO

Article history:
Received 20 July 2016
Accepted 10 August 2016

Keywords:
Arterial grafts
Coronary artery bypass grafts
Gender
Outcomes

ABSTRACT

Background: Concerns about increased risk of postoperative complications, primarily deep sternal wound infection (DSWI), prevent liberal use of bilateral internal thoracic artery (BITA) grafting in women. Consequently, outcomes after routine BITA grafting remain largely unexplored in female gender.
Methods: Of 786 consecutive women with multivessel coronary disease who underwent isolated coronary bypass surgery at the authors' institution from 1999 throughout 2014, 477 (60.7%; mean age: 70 ± 7.7 years) had skeletonized BITA grafts; their risk profiles, operative data, hospital mortality and postoperative complications were reviewed retrospectively. Risk factor analysis for hospital death, DSWI and poor late outcomes were performed by means of multivariable models.
Results: There were 19 (4%) hospital deaths (mean EuroSCORE II: 5.2 ± 6.1%); glomerular filtration rate < 50 ml/min was an independent risk factor (p = 0.035). Prolonged invasive ventilation (11.3%), multiple blood transfusion (12.1%) and DSWI (10.7%) were most frequent major postoperative complications. Predictors of DSWI were body mass index >35 kg/m^2 (p = 0.0094), diabetes (p = 0.005), non-elective surgical priority (p = 0.0087) and multiple blood transfusions (p = 0.016). The mean follow-up was 6.8 ± 4.5 years. The non-parametric estimates of the 13-year freedom from cardiac and cerebrovascular deaths, major adverse cardiac and cerebrovascular events, and repeat myocardial revascularization were 76.1 [95% confidence interval (CI): 73.1–79.1], 59.5 (95% CI: 55.9–63.1) and 91.9% (95% CI: 90.1–93.7), respectively. Preoperative congestive heart failure (p = 0.04) and left main coronary artery disease (p = 0.0095) were predictors of major adverse cardiac and cerebrovascular events.
Conclusions: BITA grafting could be performed routinely even in women. The increased rates of early postoperative complications do not prevent excellent late outcomes.

1. Introduction

In coronary artery bypass graft (CABG) surgery as well as in every cardiac operation, female gender is a predictor of poor early and late outcomes. In almost all scoring systems specifically designed to predict the operative risk after cardiac surgery, female gender is among the risk factors for hospital, or 30-day mortality [1–4]. In almost all studies reporting immediate postoperative complications and long-term outcomes after CABG surgery, the results are worst in women [5,6].

In the last decade, the use of bilateral internal thoracic artery (BITA) grafting for myocardial revascularization has proven to be useful to improve long-term survival [7–9], even for high-risk patients such as dialysis [10] or insulin-dependent patients [11]. However, the use of BITA grafting is limited, and sometimes discouraged in women because of concerns about increased risk of postoperative complications, primarily deep sternal wound infection (DSWI) [12–14]. Consequently, outcomes of routine BITA grafting remain largely unexplored in female gender. This disparity in BITA use by sex should be addressed in the interest of expanding the benefits of BITA grafting to more large number of patients.

The present authors have reviewed retrospectively their 16-year experience in routine use of BITA grafting in women. The aims of the study were to report immediate and long-term results and perform a risk factor analysis for poor outcomes.

☆ **Funding:** This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.
☆☆ **Conflicts of Interest:** None.
* Corresponding author at: Division of Cardiac Surgery, Ospedale di Cattinara, via P. Valdoni, 7, 34148 Trieste, Italy. Tel.: +39 040 399 4103; fax: +39 040 399 4995.
E-mail address: gius.gatti@gmail.com (G. Gatti).

http://dx.doi.org/10.1016/j.carrev.2016.08.001

2. Patients and methods

From January 1999 to December 2014, 786 consecutive women with multivessel coronary artery disease had isolated CABG surgery with at least one internal thoracic artery (ITA) graft at the authors' institution; in 477 (60.7%) cases, BITA grafts were used for myocardial revascularization of the antero-septal and postero-lateral cardiac walls (left-sided revascularization). The baseline characteristics and risk profiles of these BITA patients are listed in Table 1. The expected operative risk for each patient was calculated according to the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) [1].

The protocols of preoperative evaluation of the suitability of both ITAs to be used as coronary grafts, of preoperative antibiotic management and of perioperative control of hyperglycemia that were adopted at the authors' institution have been described in previous authors' reports [11,13,15]. The definitions of preoperative clinical variables and postoperative complications were the same as have been previously used by the authors [11,13,15]. All perioperative data were prospectively recorded for every patient in a computerized data registry.

Approval to conduct the study was acquired from the Hospital Ethics Committee based on retrospective data retrieval; the need for patients to provide their individual written consent was waived.

Table 1
Preoperative patients' characteristics and risk profiles[a].

Characteristic	n = 477
Age, years	70 ± 7.8 (66–76)
<60	53 (11.1)
60–69	136 (28.5)
70–79	254 (53.2)
>80	34 (7.1)
Hypertension	373 (78.2)
Former smoker	52 (10.9)
Current smoker	10 (2.1)
BMI, kg/m^2	26.7 ± 4.3 (23.6–29.3)
>30	91 (19.1)
>35	20 (4.2)
Diabetes on insulin	49 (10.3)
Diabetes on hypoglycemic agent	96 (20.1)
Serum glucose >200 mg/dl	29 (6.1)
Serum hemoglobin, g/l	12.2 ± 1.3 (11.3–13)
<12	207 (43.4)
Poor mobility[b]	6 (1.3)
Chronic lung disease[b]	23 (4.8)
GFR[c], ml/min	60.2 ± 24.5 (47.7–73)
50–85[b]	271 (56.8)
<50[b]	137 (28.7)
Chronic dialysis	10 (2.1)
Extracardiac arteriopathy[b]	123 (25.8)
Atrial fibrillation	10 (2.1)
Congestive heart failure	44 (9.2)
Unstable angina	245 (51.4)
Recent myocardial infarction[b]	117 (24.5)
Coronary artery disease	
Left main	159 (33.3)
Two-vessel	56 (11.7)
Three-vessel	344 (72.1)
LVEF, %	56.8 ± 10 (52–60)
30–50[b]	100 (21)
20–30[b]	3 (0.6)
<20[b]	3 (0.6)
Previous PCI	11 (2.3)
Previous CABG surgery (SVGs alone)	2 (0.4)
Critical state[b]	39 (8.2)
Use of IABP	13 (2.7)
Surgical priority[b]	
Elective	150 (31.4)
Urgent	322 (67.5)
Emergency	5 (1)
Expected operative risk (by EuroSCORE II[d]), %	5.2 ± 6.1 (1.9–6.2)

BMI = body mass index; CABG = coronary artery bypass grafts; EuroSCORE = European System for Cardiac Operative Risk Evaluation; GFR = glomerular filtration rate; IABP = intra-aortic balloon pumping; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; SD = standard deviation.

[a] Values are number of patients with percentage in brackets, or mean ± SD with interquartile range in brackets.

[b] Definitions were those employed for EuroSCORE II [1].

[c] The creatinine clearance rate, calculated according to the Cockcroft–Gault formula, was used for approximating the GFR.

[d] [1].

2.1. Surgery

The surgical techniques that were used have been previously described [11,13,15]. In brief, surgery was carried out via a median sternotomy with cardiopulmonary bypass and cross-clamping the aorta. Myocardial protection was achieved with multidose cold blood cardioplegia delivered in both antegrade and retrograde mode. Off-pump technique was adopted only in the presence of a diffusely atherosclerotic ascending aorta (confirmed by epiaortic ultrasonography scan). Both ITAs were harvested as skeletonized conduits with low-intensity bipolar coagulation forceps, and used as in-situ grafts when possible. The right ITA was preferentially directed to the left anterior descending coronary artery and the left ITA to the postero-lateral cardiac wall. Additional coronary bypasses were performed with saphenous vein grafts. Sometimes, the ITA was taken down and used as a free graft either from the in-situ contralateral ITA (Y-graft) or the proximal (aortic) end of a saphenous vein graft. The aortic anastomosis of every venous graft was performed during cross-clamping of the ascending aorta in on-pump technique, and during aortic side-clamping in off-pump technique (Table 2).

2.2. Follow-up

An up-to-date clinical follow-up was obtained by a telephonic interview with the patients or their family. The occurrence of at least one postoperative major adverse cardiac and cerebrovascular event (MACCE) – defined as any of the following complications from hospital discharge to follow-up: sudden death, recurrent angina, myocardial infarction, congestive heart failure, percutaneous coronary intervention, reoperation, pulmonary embolism and cerebrovascular accident – was recorded. For this study, follow-up was closed on December 1st, 2015.

2.3. Statistical methods

Values are number of patients with percentage in brackets, or mean ± standard deviation with interquartile range in brackets. Risk factors analysis both for hospital death and DSWI was performed. Clinical variables were compared using the Chi-square, the Fisher's exact or

Table 2
Operative data[a].

Data	n = 477
No. of coronary anastomoses	3.5 ± 0.9 (3–4)
With BITA graft	2.6 ± 0.7 (2–3)
With SVGs	0.9 ± 0.8 (0–1)
Use of BITA graft alone	138 (28.9)
Surgical technique	
Off-pump	34 (7.1)
Beating heart on-pump	4 (0.8)
On-pump	439 (92)
CPB time, min	97 ± 36.4 (73–115)
Aortic cross-clamping time, min	74.3 ± 25.6 (56–90)
Duration of surgery, min	273.4 ± 65.6 (236–300)

BITA = bilateral internal thoracic artery; CPB = cardiopulmonary bypass; SD = standard deviation; SVG = saphenous vein graft.

[a] Values are number of patients with percentage in brackets, or mean ± SD with interquartile range in brackets.

Table 3
Risk factors for hospital death (univariable analysis) (n = 477)[a].

Preoperative variable	Dead n = 19	Alive n = 458	OR	95% CI	p-value
Age, years	71.2 ± 9.2 (68–77.5)	70 ± 7.7 (65.2–75)	–	–	0.5
>75	10 (52.6)	137 (29.9)	2.6	1.03–6.55	0.036
Diabetes on insulin	3 (15.8)	46 (10)	1.68	0.47–5.98	0.43
Serum glucose >200 mg/dl	2 (10.5)	27 (5.9)	1.88	0.41–8.55	0.62
Chronic lung disease[b]	2 (10.5)	21 (4.6)	2.45	0.53–11.3	0.23
GFR[c], ml/min	52.8 ± 30.2 (36.4–72.7)	60.5 ± 24.2 (48.5–73)	–	–	0.18
<50[b]	11 (57.9)	126 (27.5)	3.62	1.42–9.22	0.0041
Chronic dialysis	2 (10.5)	8 (1.7)	6.62	1.31–33.6	0.056
Extracardiac arteriopathy[b]	6 (31.6)	117 (25.5)	1.35	0.5–3.62	0.59
Congestive heart failure	3 (15.8)	41 (9)	1.91	0.53–6.82	0.4
Unstable angina	11 (57.9)	234 (51.1)	1.32	0.52–3.33	0.56
Left main coronary disease	8 (42.1)	151 (33)	1.48	0.58–3.75	0.41
LVEF, %	55.8 ± 12.7 (55–60)	56.9 ± 9.9 (52–60)	–	–	0.65
<30[b]	1 (5.3)	5 (1.1)	5.03	0.56–45.3	0.22
Critical state[b]	4 (21.1)	35 (7.6)	3.22	1.01–10.2	0.06
Urgent surgical priority[b]	16 (84.2)	306 (66.8)	2.65	0.76–9.23	0.11
Expected operative risk (by EuroSCORE II[d]), %	8.8 ± 11.3 (3.3–8.8)	5.1 ± 5.8 (1.9–6.1)	–	–	0.0044

CI = confidence interval; EuroSCORE = European System for Cardiac Operative Risk Evaluation; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; OR = odds ratio; SD = standard deviation.
[a] Values are number of patients with percentage in brackets, or mean ± SD with interquartile range in brackets.
[b] Definitions were those employed for EuroSCORE II [1].
[c] The creatinine clearance rate, calculated according to the Cockcroft–Gault formula, was used for approximating the GFR.
[d] [1].

the McNemar test for dichotomous variables, and the Student's *t* or the Mann–Whitney *U*-test for continuous variables, as appropriate. Variables from univariable analysis with a p-value <0.1 were entered into a multivariable analysis (binary logistic regression model). An odds ratio (OR) with a 95% confidence interval (CI) was given for each significant variable. Non-parametric estimates and curves of freedom from all-cause death (including hospital mortality), cardiac and cerebrovascular deaths (including hospital mortality), MACCEs, heart failure hospital readmission, and repeat myocardial revascularization were generated with the Kaplan–Meier method. Comparisons between survival curves were made by the log-rank test. The Cox proportional-hazards model was used to determine the influence of patients' characteristics and operative findings on late outcomes. The hazard ratio with 95% CI was calculated for each variable. A p-value <0.05 was considered to be statistically significant. Analyses were performed with IBM SPSS Statistics (IBM Software Group).

3. Results

3.1. Early (hospital) outcomes

There were 19 (4%) hospital deaths: 14 patients, 2.9%, died within the postoperative day 30. The causes of death were: stroke (n = 2), respiratory insufficiency (n = 2), pneumonia (n = 3), low cardiac output (n = 2), intestinal necrosis (n = 1), mediastinitis (n = 1) and multiorgan failure (n = 8). According to multivariable analysis, glomerular filtration rate < 50 ml/min resulted to be predictor of hospital death (OR = 2.95, 95% CI: 1.08–8.05; p = 0.035; Table 3). Prolonged invasive ventilation, multiple blood transfusion and DSWI were most frequent major postoperative complications (Table 4). According to multivariable analysis, body mass index >35 kg/m^2 (OR = 4.15, 95% CI: 1.42–12.2; p = 0.0094), diabetes (OR = 2.44, 95% CI: 1.31–4.56; p = 0.005), non-elective surgical priority (OR = 3.31, 95% CI: 1.35–8.11; p = 0.0087) and multiple blood transfusion (OR = 2.64, 95% CI: 1.2–5.82; p = 0.016; Table 5) were predictors of DSWI.

3.2. Time-related survival

A total of 458 patients were discharged home from the hospital. For these women, the mean follow-up period was of 6.8 ± 4.5 years

Table 4
Postoperative complications and hospital course of patients[a,b].

Complication	n = 477
Neurological dysfunction	27 (5.7)
Delayed awakening	9 (1.9)
Manifest psychiatric disorder	9 (1.9)
Seizures	1 (0.2)
Stroke	8 (1.7)
Critical illness polyneuropathy	3 (0.6)
Prolonged (>48 h) invasive ventilation	54 (11.3)
Pneumonia	41 (8.6)
Permanent hemi-diaphragmatic dysfunction	1 (0.2)
Atrial fibrillation, new-onset	133/467[c] (28.5)
Myocardial infarction	12 (2.5)
Low cardiac output	19 (4)
Use of inotropes	270 (56.6)
Intra- and postoperative use of IABP	13 (2.7)
Pulmonary embolism	1 (0.2)
Acute kidney injury	29 (6.1)
Renal replacement therapy	7 (1.5)
Bleeding peptic disease	1 (0.2)
Mesenteric ischemia	2 (0.4)
Multiorgan failure	8 (1.7)
48-h Chest tube output/BSA, ml/m^2	520 ± 469.2 (278.3–621.6)
Blood transfusion	227 (47.6)
Multiple blood transfusion (>2 RBCs)	58 (12.1)
Mediastinal re-exploration for bleeding or tamponade[d]	8 (1.7)
Sternal wound infection	70 (14.7)
Superficial incisional	19 (4)
Deep incisional[e]	45 (9.4)
Mediastinitis[e]	6 (1.3)
Leg wound complication	6/339[f] (1.8)
Sepsis	6 (1.3)
Hospital stay, days	16.3 ± 22.1 (8–15)
ICU stay, days	4.3 ± 15.7 (1–3)

BSA = body surface area; DSWI = deep sternal wound infection; IABP = intra-aortic balloon pumping; ICU = intensive care unit; RBCs = packed red blood cells; SD = standard deviation.
[a] Values are number of patients with percentage in brackets, or mean ± SD with interquartile range in brackets.
[b] Definitions of postoperative complications were the same as have been previously adopted by the authors [11,13,15].
[c] Patients with preoperative stable sinus rhythm or paroxysmal atrial fibrillation.
[d] Through resternotomy or subxifoid window.
[e] DSWI.
[f] Patients who received concomitant saphenous vein grafts.

Table 5
Risk factors for DSWI (univariable and multivariable analysis) (n = 458)[a,b].

Variable	Univariable analysis			Multivariable analysis		
	DSWI n = 51	No sternal complication n = 407	p-value	OR	95% CI	p-value
Age, years	70.8 ± 6.6 (66.5–76)	70 ± 7.8 (65.5–75)	0.53	–	–	–
>70	33 (64.7)	247 (60.7)	0.58	–	–	–
BMI, kg/m^2	28.7 ± 4.8 (25.7–31.6)	26.5 ± 4.2 (23.5–29)	0.00047	–	–	–
>35	7 (13.7)	12 (2.9)	0.0025	4.15	1.42–12.2	0.0094
Diabetes	25 (49)	111 (27.3)	0.0014	2.44	1.31–4.56	0.005
Serum glucose >200 mg/dl	4 (7.8)	23 (5.7)	0.76	–	–	–
Chronic lung disease[c]	6 (11.8)	16 (3.9)	0.026	2.8	0.95–8.31	0.063
GFR[d], ml/min	61.1 ± 26.1 (49.6–75.6)	60 2 ± 4.3 (47.7–72.4)	0.78	–	–	–
<50[c]	14 (27.5)	118 (29)	0.82	–	–	–
Chronic dialysis	1 (2)	8 (2)	0.74	–	–	–
Extracardiac arteriopathy[c]	18 (35.3)	98 (24.1)	0.083	–	–	–
Congestive heart failure	8 (15.7)	34 (8.4)	0.12	–	–	–
LVEF, %	57.2 ± 8.6 (50.2–60)	56.7 ± 10 (52–60)	0.73	–	–	–
<50[c]	13 (25.5)	89 (21.9)	0.56	–	–	–
Non-elective surgical priority[c]	45 (88.2)	269 (66.1)	0.0013	3.31	1.35–8.11	0.0087
Duration of surgery (min)	288.9 ± 65.5 (245–318)	270.9 ± 66.2 (234–295)	0.067	–	–	–
>360	6 (11.8)	23 (5.7)	0.19	–	–	–
Postoperative						
Low cardiac output[e]	2 (3.9)	17 (4.2)	0.64	–	–	–
Multiple blood transfusion (>2RBCs)	14 (27.5)	41 (10.1)	0.00032	2.64	1.2–5.82	0.016
Mediastinal re-exploration for bleeding or tamponade[f]	3 (5.9)	5 (1.2)	0.049	2.97	0.5–17.6	0.23

BMI = body mass index; DSWI = deep sternal wound infection; EuroSCORE = European System for Cardiac Operative Risk Evaluation; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; RBCs = packed red blood cells; SD = standard deviation.
[a] Values are number of patients with percentage in brackets, or mean ± SD with interquartile range in brackets.
[b] Patients with superficial incisional sternal wound infection were excluded from this analysis.
[c] Definitions were those employed for the EuroSCORE II [1].
[d] The creatinine clearance rate, calculated according to the Cockcroft–Gault formula, was used for approximating the GFR.
[e] Definition was the same as has been previously adopted by the authors [11, 13, 15].
[f] Through resternotomy or subxifoid window.

(median, 6.4 years); overall, 3096.7 patient-years were reviewed. During the follow-up period, there were 80 deaths: 55 (12%) cardiac or cerebrovascular deaths and 25 (5.5%) non-cardiac and non-cerebrovascular deaths. The causes of death were: myocardial infarction (n = 25), congestive heart failure (n = 22), sudden death (n = 6), pulmonary embolism (n = 2), malignancy (n = 15), chronic renal failure (n = 6), sepsis (n = 3) and casualty (n = 1). The non-parametric estimates of the 5-, 10- and 13-year freedom from all-cause death were 88.8 (95% CI: 87.3–90.3), 77.7 (95% CI: 75.4–80) and 68.1% (95% CI: 64.8–71.4), respectively (Fig. 1A). Low glomerular filtration rate, the New York Heart Association (NYHA) class III–IV, left main coronary disease and diffusely atherosclerotic ascending aorta were independent risk factors for all-cause death. The non-parametric estimates of the 5-, 10- and 13-year freedom from cardiac and cerebrovascular deaths were 90.6 (95% CI: 89.2–92), 83.1 (95% CI: 81–85.2) and 76.1% (95% CI: 73.1–79.1), respectively (Fig. 1B). Old age and NYHA class III–IV were independent risk factors for cardiac and cerebrovascular deaths (Table 6).

3.3. Functional status

Among the hospital discharged patients, NYHA class improved from 1.3 ± 0.7, preoperatively, to 1.2 ± 0.5 (p = 0.018); the Canadian Cardiovascular Society class improved from 3.4 ± 0.7 to 1.2 ± 0.6 (p < 0.0001). Overall, 115 (25.1%) patients had 231 MACCEs – cerebrovascular accident (n = 6), sudden death (n = 8), recurrent angina (n = 41), myocardial infarction (n = 25), congestive heart failure (n = 124), pulmonary embolism (n = 2), percutaneous coronary intervention (n = 24) and reoperation (n = 1) – and 83 (18.1%) patients experienced at least one hospital readmission because of congestive heart failure (Fig. 2). NYHA class III–IV and left main coronary disease were independent risk factors for MACCEs. Chronic lung disease and left main coronary disease were independent risk factors for heart failure hospital readmission (Table 6). Among the 25 women who underwent repeat revascularization, significant lesions of BITA or saphenous vein grafts had been shown with coronary angiography in 28% (7/25) and 57.9% (11/19) of cases, respectively (p = 0.066); in 48% (12/25) of patients there were new significant lesions of the native coronary tree.

4. Discussion

According to a retrospective United States database analysis performed on 1,526,360 patients who underwent isolated CABG surgery with at least one ITA between 2002 and 2008, the rate of BITA use was 3.9% and female gender was an independent risk factor for DSWI (OR = 1.06) [14]. Based on results from a recent analysis performed by the present authors on 2872 consecutive BITA patients operated on between 1999 and 2013 in a single institution where BITA grafting is being routinely performed (>70% of all the cases of isolated CABG surgery), female gender resulted to be an even stronger predictor of DSWI (OR = 2.96) [13]. Finally, in a series of 11,922 diabetic patients who underwent primary isolated CABG surgery between 1972 and 2011, the rate of BITA use was 7.9% and female gender was an independent risk factor for DSWI (80% increased risk) [12]. These three studies, and many other reports of Literature support the evidence that: (i) women are exposed to a higher risk of DSWI after CABG surgery than men; (ii) the DSWI risk is high for women undergoing routine BITA grafting; (iii) the DSWI risk after BITA grafting could be almost prohibitive for women with diabetes. In effect, many investigators suggest to avoid use of BITA grafting for (obese) diabetic women [12,16,17], especially since the skeletonization technique of ITA harvest could not be protective for such a patients [12]; besides, the radial artery use has proven to be a safe option in female gender [18,19]. Thus, there are

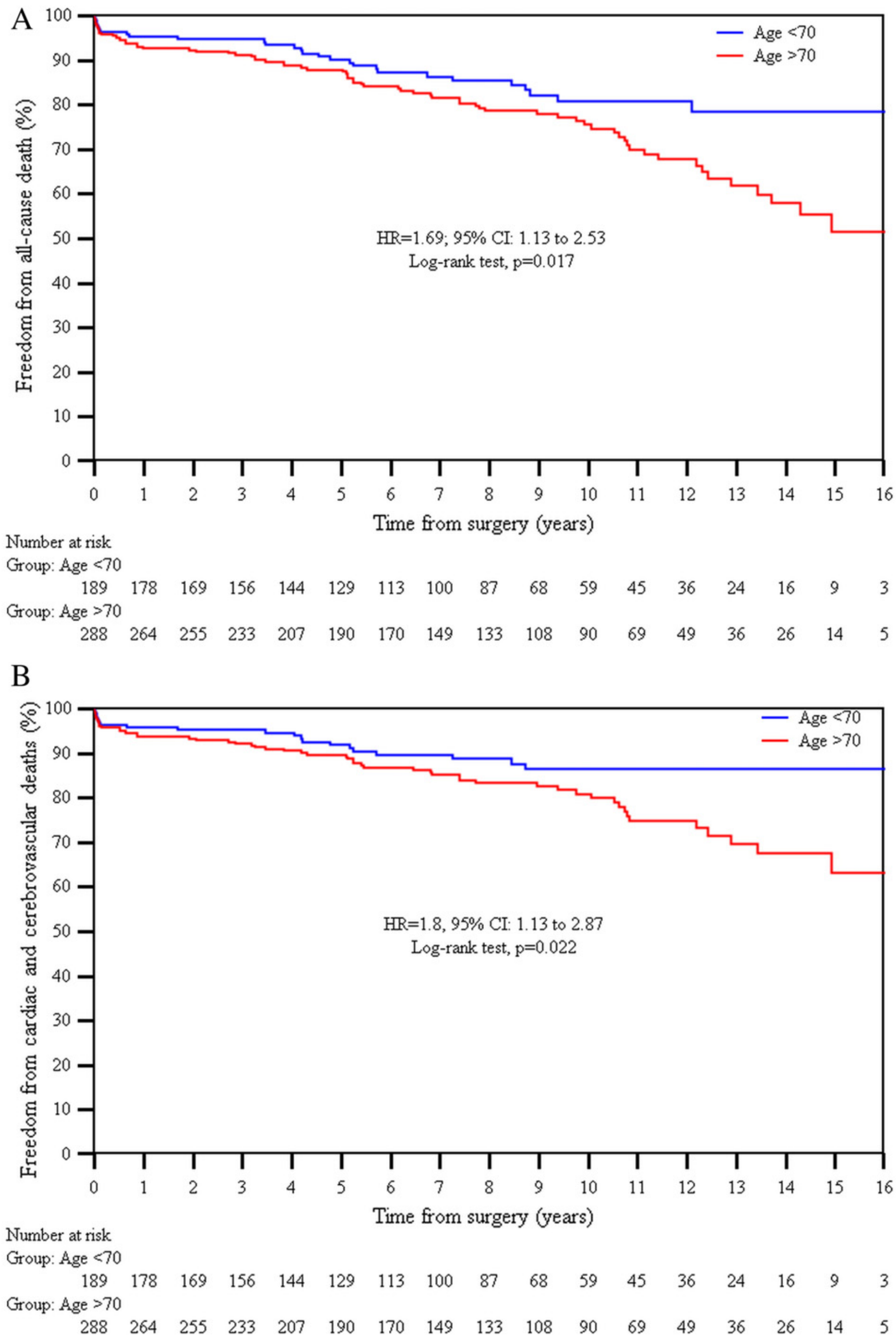

Fig. 1. Non-parametric curves of freedom from (A) all-cause death and (B) cardiac and cerebrovascular deaths (including hospital mortality) during the follow-up period. CI = confidence interval; HR = hazard ratio.

disparities in ITA use by sex and both single and bilateral ITA grafts are used less frequently in women than in men [20,21]. Consequently, outcomes of routine BITA grafting remain largely unexplored in female gender and any conclusion concerning the use of BITA grafts in women derives inevitably from clinical experiences where BITA grafting is performed in low-risk female patients [22].

Since 1986 BITA grafting has been performed routinely at the authors' institution but only since 1999 have all perioperative data for every patient been prospectively recorded in a computerized data registry. The rate of BITA use is increased from ~60% in 1999 to over 90% in 2014. All patients with multivessel coronary artery disease needing left-sided myocardial revascularization were potential candidates for BITA grafting. The sole exceptions have been: (i) the rare cases where one or both ITAs were unsuitable as coronary grafts; (ii) when there was an unexpected operative finding of severe cardiac dysfunction; (iii) when a rapid ischemic worsening of hemodynamics needed immediate institution of cardiopulmonary bypass [11,13,15]. Between 1999 and 2014, BITA grafts have been used in 74.3% of men and 60.7% of women who underwent isolated multiple CABG surgery with at least one ITA graft. Compared to other experiences on the subject [22], BITA grafts have been used more frequently, and the percent of BITA use in women was twice higher.

In the present study, outcomes of a large series of women who have undergone routine BITA grafting were specifically reviewed in order to

Table 6
Cox proportional-hazards regression for all-cause death, cardiac and cerebrovascular deaths, MACCEs, HF hospital readmission and repeat MR during the follow-up period (n = 458).

Preoperative variable	All-cause death			Cardiac and Cerebrovascular deaths			MACCEs			HF hospital readmission			Repeat MR		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age, years	1.03	0.99–1.06	0.13	1.04	1–1.09	0.032	1.01	0.99–1.04	0.36	1	0.97–1.03	0.89	0.96	0.92–1	0.058
Diabetes	1.6	1–2.55	0.051	1.41	0.8–2.49	0.24	1.29	0.86–1.94	0.22	1.1	0.68–1.78	0.69	–	–	–
Chronic lung disease[a]	0.92	0.33–2.56	0.88	–	–	–	1.51	0.7–3.29	0.3	2.54	1.15–5.62	0.022	–	–	–
GFR[b], ml/min	0.98	0.97–1	0.013	–	–	–	1	0.99–1.01	0.47	0.99	0.98–1.01	0.37	–	–	–
Extracardiac arteriopathy[a]	1.49	0.92–2.41	0.1	1.5	0.84–2.7	0.17	1.05	0.68–1.61	0.83	–	–	–	–	–	–
Congestive heart failure	2.7	1.56–4.67	0.0004	3.01	1.56–5.79	0.001	1.81	1.03–3.19	0.04	0.84	0.37–1.92	0.69	–	–	–
Left main coronary artery disease	1.61	1.02–2.54	0.042	1.42	0.82–2.48	0.22	1.66	1.13–2.43	0.0095	1.95	1.26–3.03	0.0029	1.88	0.85–4.14	0.12
LVEF, %	–	–	–	–	–	–	1.02	1–1.04	0.05	1.01	0.98–1.03	0.6	–	–	–
BITA graft alone	–	–	–	–	–	–	0.73	0.48–1.12	0.15	1	0.63–1.59	0.99	0.59	0.25–1.57	0.32
Diffusely atherosclerotic ascending aorta (by EAS)	2.27	1.22–4.21	0.0097	1.64	0.73–3.7	0.23	1.53	0.8–2.94	0.2	–	–	–	–	–	–

BITA = bilateral internal thoracic artery; CI = confidence interval; EAS = epiaortic ultrasonography scan; GFR = glomerular filtration rate; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; MACCE = major adverse cardiac and cerebrovascular event; MR = myocardial revascularization.
[a] Definitions were those employed for the EuroSCORE II [1].
[b] The creatinine clearance rate, calculated according to the Cockcroft–Gault formula, was used for approximating the GFR.

establish the risk factors for hospital mortality, DSWI and poor late results of BITA surgery in female gender. The hospital mortality was only a little lower than expected according to EuroSCORE II and glomerular filtration rate < 50 ml/min resulted to be predictor of death. The risk profiles of patients were equivalent to those of other series of women who underwent isolated CABG surgery [5,6] but higher than those of other series of women who underwent isolated BITA grafting [22]. This was due to the high mean age (over 60% of the patients had 70 years or more; about 7% were octogenarians) and the high rates of severe renal impairment and extracardiac arteriopathy. Besides, diabetes on insulin, morbid obesity, chronic lung disease, renal replacement therapy, previous CABG surgery, critical state and emergency priority were not exclusion criteria from BITA grafting for the women of this study. There were frequent postoperative complications. Prolonged invasive ventilation was favored by a history of smoking, chronic lung disease, prolonged aortic cross-clamping and cardiopulmonary bypass times, airway infections, acute kidney injury, multiple blood transfusion and mediastinal re-exploration. Fortunately, phrenic nerve paralysis was a rare and self-resolving complication and there was only one case of permanent hemi-diaphragmatic dysfunction. Blood use was increased due to preoperative anemia (chronic renal failure), perioperative bleeding and prolonged cardiopulmonary bypass time. Sternal wound infection was an expected and frequent postoperative complication. It was more frequent than reported in other series of CABG patients that include men and women (at the present authors' institution, the rate of DSWI after isolated BITA grafting in men was 3.7%) [7,14,16,17]. The higher rate of DSWI was in all probability due to the use of BITA grafts on a routine basis without any preoperative selection of candidates for left-sided BITA grafting [11,13,15]. Body mass index >35 kg/m^2, diabetes, non-elective surgical priority and multiple blood transfusion were predictors of DSWI. Chronic lung disease and mediastinal re-exploration resulted to be risk factors according to univariable but not multivariable analysis. Unlike what has previously been reported by some authors [23], off-pump surgery was not a protective factor for DSWI [14,17]. In the present study, however, off-pump technique has been used exclusively to avoid clamping a calcified ascending aorta [11,13,15]. Acute kidney injury was a relatively rare complication despite the frequent preoperative renal impairment, prolonged cardiopulmonary bypass time and multiple blood transfusion. The right ITA was preferentially used as in-situ graft (up to 80% of all cases); when the right ITA was used as a free graft, it was preferably anastomosed to the in-situ left ITA (Y-graft). Probably due to the institutional policy of reduced aortic manipulation and the routine use of epiaortic ultrasonography scanning, the rate of irreversible neurological complications was <2%.

During the follow-up period, there was a significant symptomatic improvement for the patients. Like other similar experiences on the topic [22], the estimates of the long-term freedom from all-cause death, cardiac and cerebrovascular deaths, MACCEs, heart failure hospital readmission, and repeat myocardial revascularization for these women who had undergone BITA grafting were very good. The late outcomes compared favorably with those of previous studies on CABG surgery with single ITA in women [5,6] but were equivalent to those of previous investigations on CABG surgery with left ITA and radial artery in women [18,19]. Actually, not all of these studies included hospital (or 30-day) mortality into the non-parametric estimates of survival. According to multivariable analysis, old age, chronic lung disease, low glomerular filtration rate and diffusely atherosclerotic ascending aorta were predictors of cardiac and cerebrovascular deaths, heart failure hospital readmission, all-cause death and MACCEs, respectively; NYHA class III–IV was shared predictor of all-cause death, cardiac and cerebrovascular deaths and MACCEs; left main coronary disease was shared predictor of all-cause death, MACCEs and heart failure hospital readmission. Although the use of BITA graft alone was combined with a lower risk both for MACCEs and repeat myocardial revascularization, the significance was not achieved. In effect, (i) the BITA grafting alone strategy [24] was adopted not for every patient with two-vessel coronary artery disease; (ii) one or more new significant lesions had been shown with coronary angiography not only in the native coronary tree but also in ~30% of the BITA grafts out of the patients who underwent repeat myocardial revascularization.

The primary limitation of the present study was the retrospective nature of the analysis and that the patients were evaluated at different times after surgery. No comparison was made as the results between skeletonized and pedicled BITA grafts, off- and on-pump BITA grafting or bilateral and single ITA use. Coronary angiography was performed only in few strongly symptomatic patients; there was no direct information about patency of BITA grafts in all the remaining patients. Consequently, the results obtained can in no way be considered conclusive and should be verified in a larger patient population by means of prospective controlled trials that include angiographic evaluations.

In conclusion, on the basis of the findings of the present study, BITA grafting could be performed routinely even in women. The increased rates of early postoperative complications, primarily sternal wound infections, do not prevent excellent late outcomes.

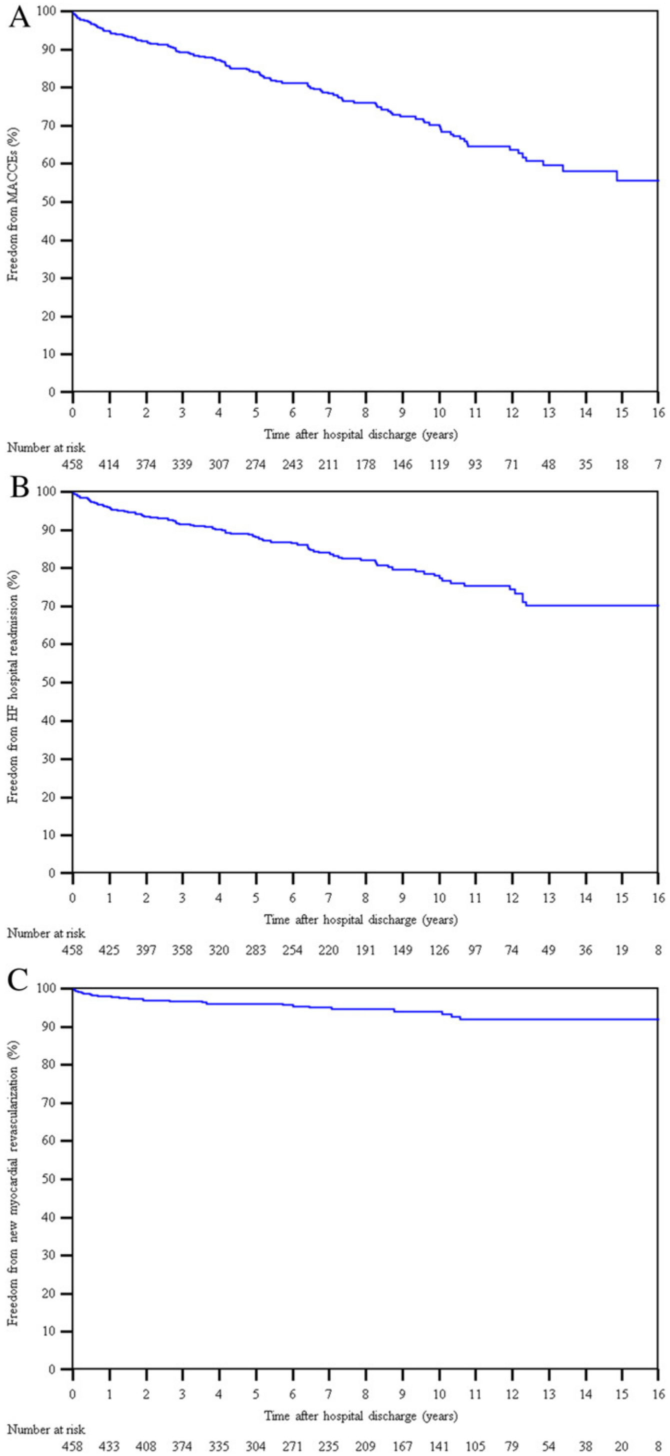

Fig. 2. Non-parametric curves of freedom from (A) MACCEs, (B) HF hospital readmission and (C) repeat myocardial revascularization during the follow-up period. The non-parametric estimates of the 5-, 10- and 13-year freedom from MACCEs were 84.1 (95% CI: 82.3–85.9), 70.2 (95% CI: 67.5–72.9) and 59.5% (95% CI: 55.9–63.1), respectively. The non-parametric estimates of the 5-, 10- and 13-year freedom from HF hospital readmission were 88.1 (95% CI: 86.5–89.7), 78 (95% CI: 75.6–80.4) and 70.1% (95% CI: 66.7–73.5), respectively. The non-parametric estimates of the 5-, 10- and 13-year freedom from repeat myocardial revascularization were 96.1 (95% CI: 95.2–97), 94 (95% CI: 92.7–95.3) and 91.9% (95% CI: 90.1–93.7), respectively. CI = confidence interval; HF = heart failure; MACCE = major adverse cardiac and cerebrovascular event.

References

[1] Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. EuroSCORE II. Eur J Cardiothorac Surg 2012;41:734–44.
[2] Tu JV, Jaglal SB, Naylor D. Multicenter validation of a risk index for mortality, intensive care unit stay, and overall hospital length of stay after cardiac surgery. Circulation 1995;91:677–84.
[3] Anderson RP. First publications from the Society of Thoracic Surgeons National Database. Ann Thorac Surg 1994;57:6–7.
[4] Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. Circulation 1989; 701:S13–112.
[5] Hassan A, Chiasson M, Buth K, Hirsch G. Women have worse long-term outcomes after coronary artery bypass grafting than men. Can J Cardiol 2005;21:757–62.
[6] Guru V, Fremes SE, Tu JV. Time-related mortality for women after coronary artery bypass graft surgery: a population-based study. J Thorac Cardiovasc Surg 2004; 127:1158–65.
[7] Benedetto U, Amrani M, Gaer J, Bahrami T, de Robertis F, Simon AR, et al. The influence of bilateral internal mammary arteries on short- and long-term outcomes: a propensity score matching in accordance with current recommendations. J Thorac Cardiovasc Surg 2014;148:2699–705.
[8] Smith T, Kloppenburg GT, Morshuis WJ. 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? Interact Cardiovasc Thorac Surg 2014;18:96–101.
[9] Popovic B, Voillot D, Maureira P, Vanhuyse F, Agrinier N, Aliot E, et al. Bilateral internal mammary artery bypass grafting: long-term clinical benefits in a series of 1000 patients. Heart 2013;99:854–9.
[10] Kai M, Okabayashi H, Hanyu M, Soga Y, Nomoto T, Nakano J, et al. Long-term results of bilateral internal thoracic artery grafting in dialysis patients. Ann Thorac Surg 2007;83:1666–71.
[11] Gatti G, Soso P, Dell'Angela L, Maschietto L, Dreas L, Benussi B, et al. Routine use of bilateral internal thoracic artery grafts for left-sided myocardial revascularization in insulin-dependent diabetic patients: early and long-term outcomes. Eur J Cardiothorac Surg 2015;48:115–20.
[12] Rubens FD, Chen L, Bourke M. Assessment of the association of bilateral internal thoracic artery skeletonization and sternal wound infection after coronary artery bypass grafting. Ann Thorac Surg 2015. http://dx.doi.org/10.1016/j.athoracsur.2015.10.031.
[13] Gatti G, Dell'Angela L, Barbati G, Benussi B, Forti G, Gabrielli M, et al. A predictive scoring system for deep sternal wound infection after bilateral internal thoracic artery grafting. Eur J Cardiothorac Surg 2016;49:910–7.
[14] Itagaki S, Cavallaro P, Adams DH, Chikwe J. Bilateral internal mammary artery grafts, mortality and morbidity: an analysis of 1 526 360 coronary bypass operations. Heart 2013;99:849–53.
[15] Gatti G, Dell'Angela L, Benussi B, Dreas L, Forti G, Gabrielli M, et al. Bilateral internal thoracic artery grafting in octogenarians: where are the benefits? Heart Vessels 2016;31:702–12.
[16] Raza S, Sabik III JF, Masabni K, Ainkaran P, Lytle BW, Blackstone EH. Surgical revascularization techniques that minimize surgical risk and maximize late survival after coronary artery bypass grafting in patients with diabetes mellitus. J Thorac Cardiovasc Surg 2014;148:1257–64.
[17] Kieser TM, Rose MS, Aluthman U, Montgomery M, Louie T, Belenkie I. Toward zero: deep sternal wound infection after 1001 consecutive coronary artery bypass procedures using arterial grafts: implications for diabetic patients. J Thorac Cardiovasc Surg 2014;148:1887–95.
[18] Dimitrova KR, Hoffman DM, Geller CM, Ko W, Lucido DJ, Dincheva GR, et al. Radial artery grafting in women improves 15-year survival. J Thorac Cardiovasc Surg 2013;146:1467–73.
[19] Schwann TA, Engoren M, Bonnell M, Clancy C, Habib RH. Comparison of late coronary artery bypass graft survival effects of radial artery versus saphenous vein grafting in male and female patients. Ann Thorac Surg 2012;94: 1485–91.
[20] LaPar DJ, Crosby IK, Rich JB, Quader MA, Speir AM, Kern JA, et al. Bilateral internal mammary artery use for coronary artery bypass grafting remains underutilized: a propensity-matched multi-institution analysis. Ann Thorac Surg 2015;100: 8–14.
[21] Tabata M, Grab JD, Khalpey Z, Edwards FH, O'Brien SM, Cohn LH, et al. Prevalence and variability of internal mammary artery graft use in contemporary multivessel coronary artery bypass graft surgery: analysis of the Society of Thoracic Surgeons National Cardiac Database. Circulation 2009;120:935–40.
[22] Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Bilateral internal mammary artery grafting reverses the negative influence of gender on outcomes of coronary artery bypass grafting surgery. Eur J Cardiothorac Surg 2013;44:54–63.
[23] Saha KK, Deval MM, Kumar A, Kaushal RP, Saha KK, Jacob RV, et al. Off-pump bilateral internal thoracic artery grafting. Heart Lung Circ 2015;24:905–11.
[24] Jeong DS, Sung K, Lee YT, Ahn JH, Carriere KC, Kim WS, et al. Pure bilateral internal thoracic artery grafting in diabetic patients with triple-vessel disease. Ann Thorac Surg 2015;100:2190–7.