

Improved late survival with arterial revascularization

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New coronary artery revascularization strategies are developing: improved quantification of coronary artery disease by the SYNTAX score, new-generation drug-eluting stents and increased use of stents for multivessel disease, ongoing evaluation of stents for left main disease, new strategies for minimally invasive coronary artery bypass grafting (CABG) including the use of robotic-assisted CABG, hybrid procedures, and off pump CABG. In comparisons of all these strategies, the impact on survival is arguably the most important parameter. It has long been accepted that using the left internal mammary artery (LIMA) to bypass the left anterior descending coronary artery (LAD) is the gold standard and may confer the survival advantage reported for CABG compared with percutaneous coronary intervention in the literature. The survival advantage of using additional arterial conduits as compared to the conventional use of LIMA with saphenous veins only has long been debated. Our study, which involved a large cohort of 8,622 patients with multivessel disease, followed over a long period of time, has shown that in primary isolated CABG surgery performed more than 15 years ago with the use of LIMA to the LAD, bypassing the non-LAD targets with at least 1 additional arterial graft, either the right internal mammary artery and/or the radial artery, was an independent predictor of increased survival during the following 15 years. The results were confirmed with both a propensity-matched analysis that included 1,153 patients in each group and a multivariate analysis that was able to control for all differences between the groups because of the power of the large cohort in this series. The significant survival advantage of coronary artery bypass surgery with the use of multiple arterial grafting cannot be ignored in patients with multivessel coronary artery disease as various revascularization strategies are considered.

Keywords: Internal mammary artery; radial artery; revascularization; saphenous vein grafts



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Introduction

Grafting the left internal mammary artery (LIMA) to the left anterior descending artery (LAD) improves survival following coronary artery bypass graft (CABG) surgery in multivessel coronary artery disease (MVCAD) (1). Survival benefit of multiple arterial (MultArt) grafting is debated, and currently performed in less than 13% of CABG operations (2).

We reviewed our results with surgical revascularization of MVCAD patients, hypothesizing that MultArt CABG would present a significant long-term survival benefit compared with conventional CABG using the LIMA to the

LAD with additional saphenous vein grafting (SVG) (3).

Methods

From January 1, 1993, to December 31, 2009, 8,622 consecutive MVCAD patients underwent isolated primary CABG either with LIMA and additional SVGs, the LIMA/SV group (n=7,435) or with MultArt grafts with or without the addition of SVGs, the MultArt group (n=1,187), including the following MultArt subgroups: bilateral internal mammary artery (BIMA)/SV (n=589) with the use of BIMA and SVGs, BIMA only (n=271), BIMA/radial artery (RA) (n=147), LIMA/RA (n=169), and BIMA/RA/SV

MultArt Subgroups n=1,187

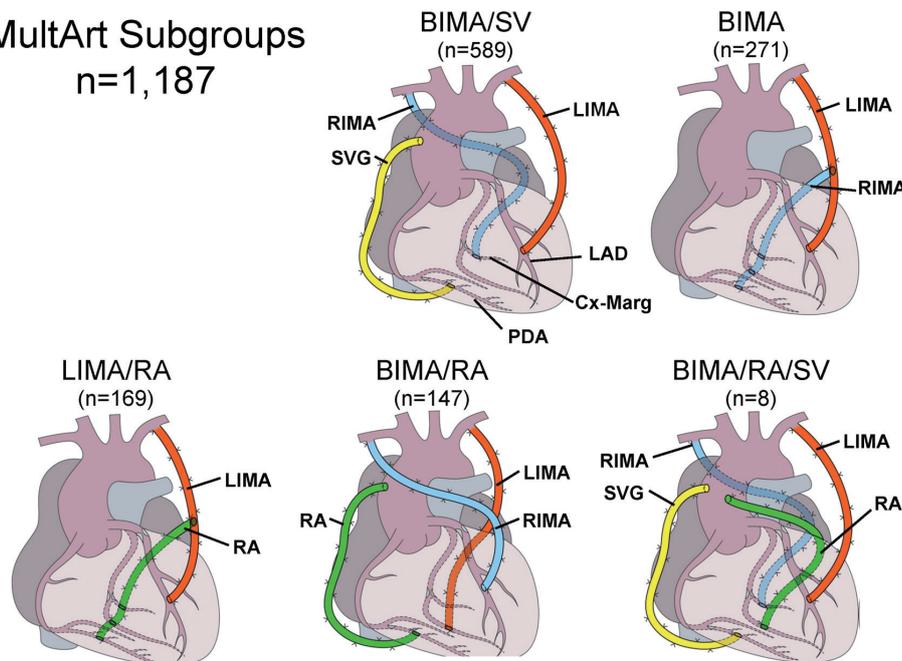


Figure 1 The 5 main surgical techniques for MultArt grafting: (I) BIMA/SV, *in situ* LIMA to LAD, *in situ* RIMA through the transverse sinus to the Cx-Marginal and SVG to PDA (n=589); (II) BIMA, composite T-grafting, LIMA to the LAD and free RIMA to the Cx-Marginal and PDA (n=271); (III) LIMA/RA, LIMA to LAD and free RA to the Cx-Marginal and PDA (n=169); (IV) BIMA/RA, *in situ* LIMA to Cx-Marginal, *in situ* RIMA to LAD and free RA to PDA (n=147); and (V) BIMA/RA/SV, LIMA to LAD, RIMA to Cx-Marginal, RA to Cx-Marginal and SVG to PDA (n=8). MultArt, multiple arterial grafting; n, number of patients; BIMA, bilateral internal mammary artery; SVG, saphenous vein graft; RA, radial artery; LIMA, left internal mammary artery; RIMA, right internal mammary artery; LAD, left anterior descending; Cx-Marg, circumflex marginal; PDA, posterior descending artery. (Reprinted from *Circulation*, Lippincott Williams & Wilkins, with permission. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information) (3)

(n=8) (Figure 1). There were 3 additional cases, 2 with the use of right internal mammary artery (RIMA)/RA, and 1 with the use of BIMA/gastroepiploic artery.

Indications for myocardial revascularization were based on the standard clinical and angiographic criteria. All patients were operated on through median sternotomy. Internal mammary arteries (IMAs) were harvested as pedicled or skeletonized conduits. IMAs and RAs were prepared with dilute topical solution of papaverine. Most of the operations were performed with standard cardiopulmonary bypass (CPB). Myocardial preservation during CPB involved intermittent, antegrade, or retrograde crystalloid or blood cardioplegia (28–32 °C).

The LIMA was grafted almost exclusively to the LAD and SVGs were grafted to the non-LAD vessels in LIMA/SV patients. The LIMA was also preferentially grafted to the LAD in MultArt patients, although occasionally it was used as an *in situ* graft to the marginal branch of

the left circumflex coronary artery (LCx) with additional use of *in situ* RIMA to the LAD. The RIMA was grafted preferentially as an *in situ* graft through the transverse sinus to the marginal branch of the LCx, as a free graft in a composite-T configuration from the side of the LIMA, or, less frequently, as a free graft from the aorta to the LCx and/or to the right coronary artery (RCA) branches. The RA was used as a free graft in a composite-T configuration from the side of the LIMA or as a free graft from the aorta, to the LCx and/or to the RCA branches. SVGs were also used in MultArt subgroups preferentially to the right coronary system and less frequently to the LCx branches, diagonal or intermediate coronary vessels.

Overall, 20% of cases in the MultArt group were grafted with one artery to the LAD and second to the RCA territory, with no additional arterial grafting to the left coronary system, and 30% of RIMA grafts and 41% of RA grafts were anastomosed to the RCA territory in the MultArt group.

Table 1 Patient characteristics[†]

Variable	Unmatched groups			Propensity score matched groups		
	LIMA/SV (n=7,435)	MultArt (n=1,187)	P value	LIMA/SV (n=1,153)	MultArt (n=1,153)	P-value
Age, y	68±9	58±9	<0.001	59±10	59±9	0.77
Female sex, %	24.8 (23.8-35.7)	15.1 (13.0-17.1)	<0.001	16.2 (14.1-18.4)	15.2 (13.1-17.3)	0.49
BSA, m ²	2.02±0.23	2.06±0.22	<0.001	2.05±0.23	2.05±0.22	0.46
EF, %	55±14	57±11	<0.001	58±13	58±11	0.77
Hypertension, %	76.6 (75.7-77.6)	66.6 (64.0-69.3)	<0.001	68.7 (66.0-71.4)	67.1 (64.4-69.8)	0.42
Diabetes mellitus, %	33.5 (32.4-34.5)	18.1 (15.9-20.3)	<0.001	19.2 (16.9-21.4)	18.5 (16.2-20.7)	0.67
Chronic lung disease, %	11.7 (10.9-12.4)	7.0 (5.5-8.4)	<0.001	7.5 (5.9-9.0)	7.0 (5.6-8.5)	0.68
Renal failure, %	5.4 (4.9-5.9)	1.9 (1.2-2.3)	<0.001	1.9 (1.1-2.7)	2.0 (1.1-2.8)	0.88
PVD, %	21.5 (20.6-22.4)	13.2 (11.3-15.2)	<0.001	14.8 (12.8-16.9)	13.5 (11.6-15.5)	0.37
S/P MI, %	47.1 (45.9-48.1)	36.5 (33.7-39.1)	<0.001	38.1 (35.3-45.9)	36.8 (34.0-39.6)	0.52
S/P CVA, %	7.1 (6.5-7.7)	4.0 (2.9-5.2)	<0.001	4.5 (3.3-5.7)	4.1 (2.9-5.2)	0.60

[†]Continuous variables are expressed as mean ± SD and categorical variables as percent (95% CI). Abbreviations: LIMA, left internal mammary artery; SV, saphenous vein; MultArt, multiple arterial grafting; BSA, body surface area; EF, ejection fraction; PVD, peripheral vascular disease; S/P MI, status post myocardial infarction; S/P CVA, status post cerebral vascular accident. (Reprinted from *Circulation*, Lippincott Williams & Wilkins, with permission. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information) (3)

With approval of the Mayo Clinic Institutional Review Board and after obtaining patient consent, data were collected retrospectively by reviewing our clinical charts and computerized cardiac surgery database. Patient data were analyzed according to the Society of Thoracic Surgeons National Cardiac Surgery Database definitions. Follow-up was obtained by clinical chart review, mailed questionnaires, and the Social Security Death Index.

Descriptive statistics for categorical and continuous variables were reported as frequency and percentage, and as mean (SD), respectively. Categorical and continuous baseline variables were compared between MultArt and LIMA/SV patients by using χ^2 test and 2 sample *t*-test or Wilcoxon rank sum test, respectively.

Logistic regression models were used to find univariate and multivariate predictors of operative mortality. Kaplan-Meier method was used to draw survival curves and calculate 5-, 10-, and 15-year survival statistics. Cox regression models were used to find the univariate and multivariate predictors of late survival and overall survival. The multivariable model considered all univariate significant variables ($P < 0.05$) with model selection using the stepwise method. A propensity score was calculated for each patient, and 2 groups with matched propensity scores were selected. Late survival was then compared between the

matched groups using Kaplan-Meier estimates and curves. All statistical tests were two-sided with the alpha level set at 0.05 for statistical significance.

Results

The clinical characteristics and operative variables of MultArt group and LIMA/SV group are shown in *Tables 1, 2*, respectively. There were significant differences between the 2 unmatched groups. Aortic cross clamp time was similar in both groups (50±19 min) and bypass time was slightly longer in LIMA/SV group compared to MultArt group (85±31 and 75±30 min, respectively).

Propensity score analysis matched 1,153 patients from each group, including 97.2% of MultArt group and 15.5% of LIMA/SV group. Unadjusted operative mortality was 0.8% in MultArt group and 2.1% in LIMA/SV group ($P = 0.005$); however, was not significantly different after multivariate adjustment or propensity score matching ($P = 0.996$ and matched mortality 0.9% vs. 0.8%, $P = 0.818$; respectively). In patients without operative deaths ($n = 8,458$), follow-up ranged from 3 days to 18.3 years, with a mean of 7.6 years (SD=4.6) and median of 7.3 years. Follow-up beyond 30 days included 7,951 patients (94%).

Kaplan-Meier estimated 15-year survival rates were

Table 2 Operative variables[†]

Variable	Unmatched groups			Propensity score matched groups		
	LIMA/SV (n=7,435)	MultArt (n=1,187)	P value	LIMA/SV (n=1,153)	MultArt (n=1,153)	P-value
OPCAB	4.4 (4.0-4.9)	3.3 (2.3-4.3)	0.07	3.6 (2.6-4.7)	3.3 (2.3-4.3)	0.65
Urgent/Emergent	26.0 (24.3-26.2)	25.0 (22.0-26.9)	0.55	26.2 (23.7-28.7)	24.3 (21.86-26.8)	0.29
LM disease >50%	33.4 (32.3-34.4)	34.0 (30.8-36.2)	0.84	33.6 (30.8-36.3)	33.1 (30.8-36.3)	0.82
2-VSD	17.3 (16.4-18.1)	26.3 (23.8-28.8)	<0.001	25.3 (22.8-27.8)	26.0 (23.5-28.6)	0.71
3-VSD	83.0 (81.9-83.6)	74.0 (71.2-76.2)	<0.001	74.7 (72.2-77.2)	74.0 (71.5-76.5)	0.70
2 distals	15.5 (14.6-16.3)	21.0 (18.5-23.1)	0.003	21.2 (18.8-23.5)	20.5 (18.1-22.8)	0.68
3 distals	49.3 (48.1-50.4)	44.6 (41.7-47.4)	<0.001	45.4 (42.6-48.3)	44.7 (41.8-47.5)	0.71
4 or more distals	35.3 (34.2-36.4)	34.6 (31.9-37.3)	0.65	33.4 (30.7-36.1)	35.0 (32.1-37.6)	0.45

[†]Variables are expressed as percent (95% CI). Abbreviations: LIMA, left internal mammary artery; SV, saphenous vein; MultArt, multiple arterial grafting; n, number of patients; OPCAB, off-pump coronary artery bypass; Urgent/Emergent, surgical priority; LM, left main; VSD, vessel disease; distals, distal anastomoses. (Reprinted from *Circulation*, Lippincott Williams & Wilkins, with permission. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information) (3)

Late survival MultArt vs. LIMA/SV

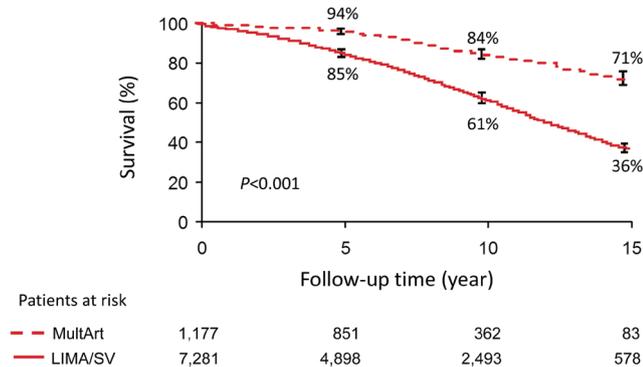


Figure 2 Kaplan-Meier curve for late survival for MultArt vs. LIMA/SV Unmatched Groups: MultArt (dashed line) vs. LIMA/SV (solid line); hazard ratio (HR) 0.33; 95% confidence interval 0.28-0.39; $P < 0.001$. MultArt, multiple arterial grafting; LIMA, left internal mammary artery; SV, saphenous vein. (Reprinted from *Circulation*, Lippincott Williams & Wilkins, with permission. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information) (3)

significantly higher for patients with MultArt grafts compared to LIMA/SV group [5-, 10-, and 15-year survival rates were 95%, 84%, and 71% vs. 85%, 61%, and 36%, respectively ($P < 0.001$) in the unmatched groups, and

Late survival MultArt vs. LIMA/SV matched group

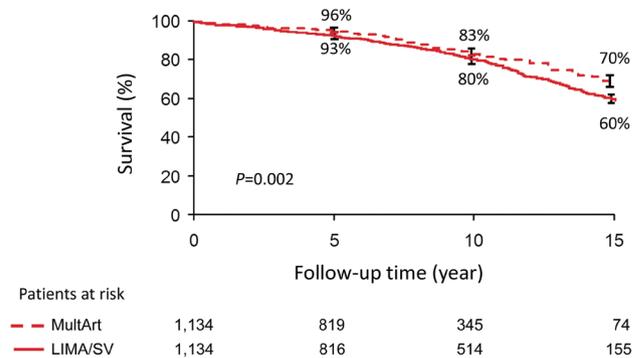


Figure 3 Kaplan-Meier curve for late survival for MultArt vs. LIMA/SV Propensity Score Matched Groups: MultArt (dashed line) vs. LIMA/SV (solid line); hazard ratio (HR) 0.73; 95% confidence interval 0.59-0.90; $P = 0.003$. MultArt, multiple arterial grafting; LIMA, left internal mammary artery; SV, saphenous vein. (Reprinted from *Circulation*, Lippincott Williams & Wilkins, with permission. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information) (3)

96%, 83% and 70% vs. 93%, 80% and 60%, respectively ($P = 0.0025$) in the propensity score matched groups (Figures 2,3)]. Importantly, in both figures, the cumulative survival curve of LIMA/SV group exhibits clear downsloping, and

Table 3 Kaplan-Meier estimated late survival rates: MultArt subgroups vs. LIMA/SV (P<0.001)

	1 y/s, %	5 y/s, %	10 y/s, %	15 y/s, %
BIMA/SV (n=583)	98.7 (97.8-99.7)	96.5 (94.9-98.1)	85.8 (82.1-89.6)	75.8 (69.8-82.3)
BIMA/RA (n=145)	99.2 (97.8-100.0)	95.1 (91.4-99.0)	84.3 (76.6-92.7)	NA
BIMA (n=270)	99.2 (98.1-100.0)	96.5 (91.4-97.6)	82.0 (75.5-89.1)	74.5 (63.1-88.1)
LIMA/RA (n=168)	99.4 (98.2-100.0)	93.4 (89.5-97.4)	78.4 (70.8-86.9)	NA
LIMA/SV (n=7,281)	97.5 (97.1-97.9)	85.0 (84.1-85.9)	61.1 (59.8-62.5)	36.3 (34.6-38.1)

Abbreviations: MultArt, multiple arterial grafting; LIMA, left internal mammary artery; SV, saphenous vein; y/s, year/survival; BIMA, bilateral internal mammary artery; RA, radial artery; NA, not available. Values in parentheses are 95% confidence intervals. (Reprinted from *Circulation*, Lippincott Williams & Wilkins, with permission. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information) (3)

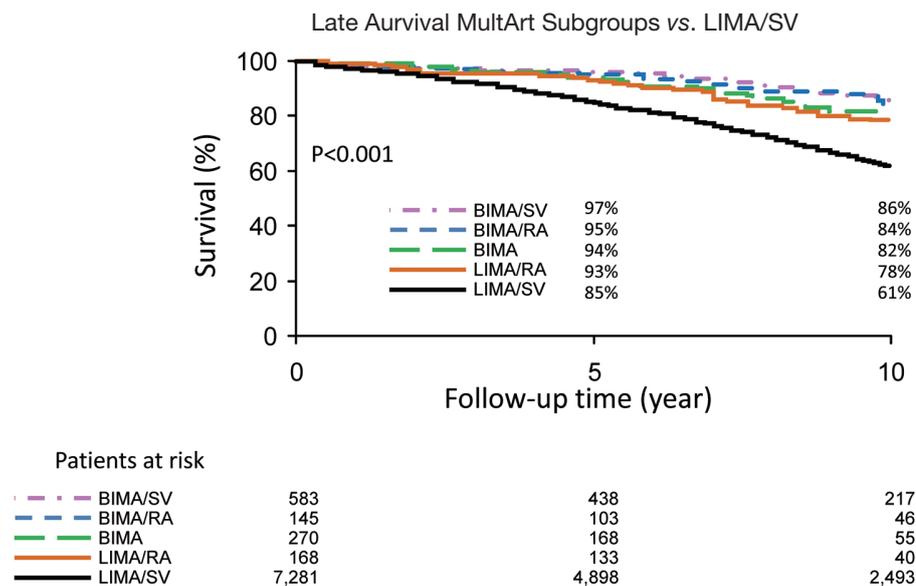


Figure 4 Kaplan-Meier curve for late survival for MultArt subgroups vs. LIMA/SV. Unmatched Groups: BIMA/SV (dashed dotted line) vs. LIMA/SV (solid line); hazard ratio (HR) 0.27; 95% confidence interval (CI) 0.21-0.37; P<0.001. BIMA/RA (dashed line) vs. LIMA/SV (solid line); HR 0.35; 95% CI, 0.21-0.56; P<0.001. BIMA (wide dashed line) vs. LIMA/SV (solid line); HR 0.37; 95% CI, 0.25-0.54; P<0.001 and LIMA/RA (dashed double dotted line) vs. LIMA/SV (solid line); HR 0.56; 95% CI, 0.36-0.79; P<0.001. MultArt, multiple arterial grafting; LIMA, left internal mammary artery; SV, saphenous vein; BIMA, bilateral internal mammary artery; RA, radial artery. (Reprinted from *Circulation*, Lippincott Williams & Wilkins, with permission. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information.) (3)

more accelerated separation of the 2 curves around 10 years.

MultArt subgroups with the use of BIMA/SV and BIMA, had late survival rates of 97% and 94% at 5 years; 86% and 82% at 10 years; and 76% and 75% at 15 years, respectively (P<0.001); and subgroups with the use of BIMA/RA and LIMA/RA had late survival rates of 95% and 93% at 5 years, and 84% and 78% at 10 years, respectively

(P<0.001) (Table 3 and Figure 4). BIMA/RA/SV subgroup had too few patients to be included in analysis.

Almost all differences in patient characteristics and operative variables were identified as predicting late death in univariate Cox regression models due to the large cohort size, enabling us to include and control for all those characteristics and variables in the multivariate analysis.

Table 4 Late death in MultArt vs. LIMA/SV: multivariate regression model

Variable	HR (95% CI)	P value
MultArt vs. LIMA/SV	0.79 (0.66-0.94)	0.007
Older age (per 1 y)	1.07 (1.06-1.07)	<0.001
Lower EF (per 1%)	1.02 (1.02-1.03)	<0.001
Hypertension	1.14 (1.04-1.24)	0.004
Diabetes mellitus	1.55 (1.43-1.67)	<0.001
Chronic lung disease	1.64 (1.49-1.82)	<0.001
Renal failure	2.28 (1.99-2.60)	<0.001
PVD	1.45 (1.34-1.57)	<0.001
S/P MI	1.10 (1.02-1.19)	0.013
S/P CVA	1.56 (1.38-1.77)	<0.001
LM disease >50%	1.17 (1.08-1.26)	<0.001
Urgent/Emergent	1.11 (1.01-1.22)	0.030
OPCAB	1.32 (1.12-1.54)	<0.001

Abbreviations: MultArt, multiple arterial grafting; LIMA, left internal mammary artery; SV, saphenous vein; HR, hazard ratio; CI, confidence interval; EF, ejection fraction; PVD, peripheral vascular disease; S/P MI, status post myocardial infarction; S/P CVA, status post cerebral vascular accident; LM, left main; Urgent/Emergent, surgical priority; OPCAB, off pump coronary artery bypass. (Reprinted from *Circulation*, Lippincott Williams & Wilkins, with permission. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information) (3)

Older age, lower ejection fraction, hypertension, diabetes, chronic lung disease, renal failure, peripheral vascular disease, previous myocardial infarction, previous cerebral vascular accident, clinically important stenosis in the left main coronary artery, urgent/emergent surgical priority, off-pump coronary artery bypass (OPCAB), and absence of MultArt grafts were identified by multivariate Cox regression model as significant independent predictors of late death (*Table 4*).

The presence of MultArt grafts reduced the risk of dying by a factor of 0.79 (95% CI, 0.66-0.94) and was identified as a significant independent predictor of survival (P=0.007). Subsets of MultArt patients had significantly higher estimated rates of survival at 15 years (*Table 5*) (P<0.001).

The analysis was stratified by year of surgery, before

and after 2001. MultArt group had better late survival rates compared to LIMA/SV group in both eras.

Discussion

This large cohort study has shown that in primary isolated CABG performed more than 15 years ago with the use of LIMA to the LAD, bypassing the non-LAD targets with at least 1 additional arterial graft was a strong independent predictor of survival during the following 15 years. The improved survival was seen among several subsets of patients that are currently excluded at many centers from being considered to receive MultArt grafting, including patients with female sex, age older than 65 years, impaired left ventricular function, diabetes mellitus, chronic lung disease, renal failure, clinically significant left main disease, double and triple vessel disease, and those operated on with urgent/emergent surgical priority.

Long-term survival after CABG is considered to be in linear correlation with late patency of the selected conduits and grafts constructed (4). Thus, the superiority in long-term survival observed among MultArt patients, compared with LIMA/SV patients, may be related to the accelerated atherosclerosis of vein grafts with their higher rates of subsequent closure around 10 years (5). Arterial grafts possess various mechanisms that lead to increased blood flow and resistance to atherosclerosis (6).

These results, showing superior late survival with MultArt grafting, imply that the initial selection of MultArt conduits has a major influence on late survival after CABG.

The study was observational and retrospective. Thus, we cannot exclude the role of selection preferences that could contribute to improved results in the MultArt group. However, the multivariate analysis is particularly striking because of the power obtained by a very large cohort of patients, which allowed controlling for all differences between the groups. Propensity matched analysis included almost all MultArt patients and demonstrated a significant independent survival benefit associated with the use of MultArt grafting.

In conclusion, this study shows that MultArt grafting is a very important underutilized surgical tool that must be considered in all MVCAD patients, aiming to significantly improve their long-term survival.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

Table 5 Kaplan-Meier estimated survival rates at 15 years: MultArt vs. LIMA/SV (P<0.001)

	MultArt			LIMA/SV		
	n	Survival (%)	95% CI (%)	n	Survival (%)	95% CI (%)
Sex						
Male	1,008	73	67-79	5,594	37	35-39
Female	179	57	43-76	1,841	32	29-36
Age						
<65	908	82	77-86	2,410	59	56-62
>65	279	32	21-49	5,025	24	22-26
EF						
Normal	439	77	70-85	2,511	44	42-47
Impaired	748	66	59-74	4,924	31	29-33
Diabetes mellitus						
Yes	215	57	44-74	2,488	27	24-30
No	972	73	67-79	4,944	39	37-42
Chronic lung disease						
Yes	83	72	61-86	867	18	14-22
No	1,104	70	65-76	6,560	38	36-40
Renal failure						
Yes	23	39	18-86	400	3	1-8
No	1,163	72	66-77	7,034	37	36-39
LM disease>50%						
Yes	398	72	64-81	2,475	32	29-35
No	784	70	64-77	4,940	37	35-39
3-VSD						
Yes	875	69	63-76	6,152	35	33-36
2-VSD						
Yes	312	73	64-84	1,283	40	36-45
Urgent/emergent						
Yes	290	73	63-84	1,877	33	29-38
No	897	71	65-77	5,558	36	35-38

Abbreviations: MultArt, multiple arterial grafting; LIMA, left internal mammary artery; SV, saphenous vein; CI, confidence interval; EF, ejection fraction; LM, left main; VSD, vessel disease; Urgent/Emergent, surgical priority. (Reprinted from *Circulation*, Lippincott Williams & Wilkins, with permission. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@lww.com for further information) (3)

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