

Incremental Value of Increasing Number of Arterial Grafts: The Effect of Diabetes Mellitus



Thomas A. Schwann, MD, Abdul Karim M. El Hage Sleiman, MD, Maroun B. Yammine, MD, Robert F. Tranbaugh, MD, Milo Engoren, MD, Mark R. Bonnell, MD, and Robert H. Habib, PhD

Department of Surgery, University of Toledo College of Medicine and Life Sciences, Toledo, Ohio; Department of Surgery, Mercy Saint Vincent Medical Center, Toledo, Ohio; Department of Internal Medicine, Outcomes Research Unit, American University of Beirut, Beirut, Lebanon; Scholars in Health Research Program, American University of Beirut, Beirut, Lebanon; Department of Surgery, Weill Cornell Medical College, New York, New York; Department of Anesthesiology, University of Michigan Medical Center, Ann Arbor, Michigan; and The Society of Thoracic Surgeons Research Center, Chicago Illinois

Background. Multiarterial coronary grafting with two arterial grafts leads to improved survival compared with conventional single artery based on left internal thoracic artery to left anterior descending artery and saphenous vein grafts. We investigated whether extending arterial grafting to three or more arterial grafts further improves survival, and whether such a benefit is modified by diabetes mellitus.

Methods. We analyzed 15-year coronary artery bypass graft surgery mortality data in 11,931 patients (age 64.3 ± 10.5 years; 3,484 women [29.2%]; 4,377 [36.7%] with diabetes mellitus) derived from three US institutions (1994 to 2011). All underwent primary isolated left internal thoracic artery to left anterior descending artery grafting with at least two grafts: one artery ($n = 6,782$; 56.9%); two arteries ($n = 3,678$; 30.8%); or three or more arteries ($n = 1,471$; 12.3%). Long-term survival was estimated by Kaplan-Meier methods. Propensity score matching and comprehensive covariate adjustment (Cox regression) were used to derive long-term risk-adjusted hazard ratio (HR) with 95% confidence interval (CI) for increasing number of arterial grafts in the overall cohort and for diabetes and no-diabetes cohorts.

Results. Radial artery (94%) and right internal thoracic artery (6%) were used as additional arterial grafts. Multivariate analysis in all patients showed that diabetes

was associated with decreased survival (HR 1.43, 95% CI: 1.34 to 53), whereas increasing number of arterial grafts was associated with decreased mortality (one artery HR 1.0 [reference]; two arteries HR 0.87, 95% CI: 0.80 to 0.95; and three arteries HR 0.83, 95% CI: 0.72 to 0.95). Pairwise comparisons also showed an incremental benefit of additional arterial grafts: two arteries versus one artery, HR 0.89 (95% CI: 0.80 to 0.98); and three arteries versus one artery, HR 0.80 (95% CI: 0.68 to 0.94). A three-artery versus two-artery survival advantage trend was also noted, but was not significant in either the overall study cohort (HR 0.90, 95% CI: 0.75 to 1.07), the diabetes cohort (HR 0.79, 95% CI: 0.60 to 1.03), or the no-diabetes cohort (HR 0.90, 95% CI: 0.79 to 1.26). Among diabetes patients, the survival advantage of two arteries versus one artery was modest (HR 0.96, 95% CI: 0.72 to 1.11), whereas it was significant for three arteries versus one artery (HR 0.74, 95% CI: 0.58 to 0.96). Analyses of propensity matched subcohorts were also consistent.

Conclusions. Increasing number of arterial grafts improves long-term survival and supports extended use of arterial grafts in coronary artery bypass graft surgery, irrespective of diabetes status.

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Coronary artery bypass graft surgery (CABG) is one of the most frequently performed operations in the United States. For more than 2 decades, the left internal thoracic artery (LITA) to left anterior descending artery (LAD) graft has been the cornerstone of standard care for surgically treated patients with multivessel coronary artery disease. A large number of studies have since

shown that a second arterial graft further improves survival [1–6]. Yet, extended use of arterial conduits in CABG beyond the LITA-LAD graft has been slow and at times counterintuitive. In addition, little is known whether there is a specific number of arterial grafts beyond which no further survival benefit is achieved.

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Address correspondence to Dr Schwann, University of Toledo College of Medicine and Life Sciences, Toledo, OH 43615; email: thomas.schwann@utoledo.edu.

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Abbreviations and Acronyms

ACSD	= Adult Cardiac Surgery Database
BITA	= bilateral internal thoracic arteries
CABG	= coronary artery bypass graft surgery
CI	= confidence interval
CRI	= completeness of revascularization index
DM	= diabetes mellitus
HR	= hazard ratio
LAD	= left anterior descending artery
LITA	= left internal thoracic artery
RA	= radial artery
STS	= The Society of Thoracic Surgeons
SVG	= saphenous vein graft

Based on The Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database (ACSD), which is representative of 90% to 95% of the overall CABG in the United States [7], 90% of CABG patients receive a traditional single arterial operation where the LITA-LAD is supplemented by a saphenous vein graft (SVG) [8]. Counter to the growing and compelling evidence in the literature, this multiarterial CABG rate is about half the rate reported in the STS-ACSD in the early 2000s [8]. Furthermore, the use of three or more arterial grafts is extremely rare in the STS-ACSD experience, at only 0.5% of patients [8]. It is noteworthy that these CABG practice patterns in the United States are opposite to the trends in Europe, Australia, and elsewhere worldwide [8].

There are only a handful of studies focusing on the effects of extended use of arterial grafting beyond two, and hence, little guidance for the clinician on how to optimally revascularize multivessel coronary artery disease patients. The limited number of studies addressing this issue offer contradictory results [9–17], with some observing improved [10, 11, 13, 16], equivalent [9, 12, 14, 17], or worse [15] survival associated with using a third arterial graft. To clarify this, we used our multiinstitutional experience with LITA-based CABG, distinct in its relatively high use of multiarterial grafting, to compare long-term survival of patients undergoing traditional LITA-based one-artery CABG with that of patients receiving two-artery or three-artery or more bypass grafts. Here, we aimed to test the primary hypothesis that construction of a third arterial graft will provide an incremental long-term survival benefit compared with one-artery and two-artery grafts. A second aim of the current analysis was to elucidate whether—and if so, to what degree—is this incremental survival benefit derived from arterial grafts modified by diabetes mellitus (DM).

Patients and Methods

This investigation is a retrospective analysis of three institutional cardiac surgery databases collected prospectively, at two Ohio centers in accordance with the STS-ACSD definitions and criteria and at a New York center in accordance with the New York State

Department of Health Cardiac Surgery Reporting System. This retrospective analysis was approved by the corresponding Institutional Review Boards. Additional review of hospital records or interviews of patients was not needed, and informed consent requirement was waived.

Patients and Study Groups

Our analysis included patients undergoing primary nonsalvage CABG (1994 to 2011) who had at least two grafts including a LITA-LAD. Patients were excluded in case of previous or salvage CABG, or concomitant aortic, valvular, or adult congenital corrective cardiac surgery. Patients were retained in case of concurrent coronary or carotid endarterectomy, or both, or atrial fibrillation ablation. Patients with a recent (less than 24 hours) myocardial infarction or preoperative renal failure were also excluded. The study population consisted of 11,931 patients and was stratified according to DM status: DM, $n = 4,377$ (36.7%); and no-DM, $n = 7,554$ (63.3%). Patients in each of the diabetes status subcohorts were subsequently divided into groups by grafting techniques, as follows: (1) DM patients who received one-artery grafts ($n = 2,521$ [57.6%]), two-artery grafts ($n = 1,339$ [30.6%]), or three or more artery grafts ($n = 517$ [11.8%]); and (2) no-DM patients who received one-artery ($n = 4,261$ [56.4%]), two-artery ($n = 2,339$ [31.0%]), or three-artery ($n = 954$ [12.6%]) grafts. All patients receiving three or more arterial grafts were binned into the three-artery group.

Surgery and Follow-Up

The surgical techniques in these patient series have been previously reported [3, 5]. Briefly on-pump techniques were utilized in the majority of patients (more than 95%) and aortocoronary grafting was the approach of choice (more than 95%). Long-term mortality data were secured from institutional follow-ups, and from recurrent (last November 2011) searches of the US Social Security Death Index database (<http://ssdi.genealogy.rootsweb.com>). The available study follow-up period ranged between 3 and 189 months.

Propensity Score Model and Matching

For both the DM and no-DM cohorts, the one-, two-, and three-artery subgroups exhibited significant differences in their demographics, risk factors, and operative factors (Table 1). To account for this imbalance and associated confounding of outcomes analyses, we used propensity score matching to derive equally sized subcohorts of matched pairs that are balanced for all these patient and operative factors. This process was repeated six times—six propensity models: three comparisons (one artery versus two arteries; one artery versus three arteries; two arteries versus three arteries), each repeated twice for DM and no-DM—to allow for the various distinct comparisons within each of the diabetes status arms. The propensity score, or the probability that a patient received treatment for each comparison, was derived through separate nonparsimonious binary logistic regression models in which the higher number of arterial grafts was

Table 1. Patient Demographics, Risk Factors, and Operative Variables Comparing One-, Two-, and Three-Artery Diabetes and No-Diabetes Groups

Patient Factors	No-Diabetes Group				Diabetes Group			
	1 Artery (n = 4,261)	2 Arteries (n = 2,339)	3 Arteries (n = 954)	p Value	1 Artery (n = 2,521)	2 Arteries (n = 1,339)	3 Arteries (n = 517)	p Value
Categoric variables, %								
Female	30.5	19.5	13.7	<0.001	41.9	30.4	26.7	<0.001
Body mass index, kg/m ²				<0.001				<0.001
<25	27.4	18.7	19.2		19.7	10.3	15.9	
25-29.99	42.5	41.9	44.8		35.7	32.0	31.9	
30-34.99	21.8	25.5	22.7		27.5	30.8	28.0	
35-39.99	6.2	9.3	9.6		11.1	16.7	15.7	
≥40	2.1	4.6	3.7		6.0	10.2	8.5	
Hypertension	74.2	72.7	64.0	<0.001	83.5	80.7	74.7	<0.001
Peripheral vascular disease	13.3	8.6	7.0	<0.001	19.2	12.8	11.6	<0.001
Cerebrovascular disease	20.8	11.7	8.5	<0.001	25.5	14.9	12.8	<0.001
COPD	25.5	17.6	14.3	<0.001	26.2	19.3	17.0	<0.001
Myocardial infarction	55.9	50.4	48.6	<0.001	57.1	51.0	52.0	0.001
Congestive heart failure	10.9	6.1	4.2	<0.001	20.5	11.7	9.5	<0.001
Previous PCI	15.4	18.6	18.6	0.001	18.8	20.3	20.5	0.414
Three-vessel disease	75.5	78.3	82.5	<0.001	80.3	81.4	87.2	0.001
Left main disease	29.6	25.6	30.1	0.001	25.6	22.2	23.4	0.056
Emergency	8.4	6.1	4.7	<0.001	5.6	3.4	2.9	0.001
Nonisolated CABG	8.6	7.4	8.2	0.342	11.1	10.9	13.3	0.554
Continuous variables, mean ± SD								
Age, years	67.9 ± 10.2	60.4 ± 10.2	59.2 ± 10.2	<0.001	66.6 ± 9.4	60.9 ± 9.3	60.1 ± 9.1	<0.001
Body surface area, m ²	1.93 ± 0.23	2.03 ± 0.24	2.04 ± 0.24	<0.001	1.97 ± 0.25	2.07 ± 0.26	2.06 ± 0.27	<0.001
Ejection fraction	49 ± 12	49 ± 11	50 ± 11	0.007	47 ± 13	48 ± 11	49 ± 11	<0.001

CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; PCI = percutaneous coronary intervention.

always considered as the treatment group. All propensity models were based on a total of 21 variables, including a completeness of revascularization index (CRI) factor and year of surgery as well as all variables listed in Table 1 regardless of their level of statistical significance. The CRI was defined as the difference between the number of grafts and the number of diseased coronary artery systems. Patients were assigned to one of the four CRI categories: CRI = -1 or less; CRI = 0; CRI = +1; and CRI = +1 or more. Highly collinear variables were avoided. The resulting propensity scores were distinctly different for the two grafting arms in all comparisons. A custom-made computer algorithm was used to obtain groups of greedy one-to-one propensity matched pairs to within a difference of ± 1% of the propensity score.

Statistical Methods

Categorical variables were summarized as counts with percentages and compared across subgroups using the χ^2 test. Continuous variables were reported as mean ± SD and compared by unpaired Student's *t* test or the Mann-Whitney rank sum test based on normality of data. Survival data were calculated using the Kaplan-Meier product limit method to estimate unadjusted survival and compared by log rank test. Quantifying the incremental effects of one-, two-, or three-artery grafts was

achieved by deriving associated risk adjusted hazard ratio (HR) with 95% confidence interval (CI) using Cox regression analysis as follows: (1) in all patients irrespective of diabetes status (three arterial grafting categories, with one artery as reference) with comprehensive risk adjustment including all variables in Table 1 in addition to CRI and diabetes status (covariate-adjusted); (2) covariate-adjusted pairwise (two arterial categories per analysis) HRs overall and repeated for DM and no-DM strata; and (3) pairwise matched-adjusted HRs done on all propensity matched patients and then separately for the matched DM and no-DM subcohorts. A two-sided *p* value of 0.05 was adopted to indicate significance in all cases. Analyses were done using IBM SPSS Statistics 21.0 software (IBM Corporation, Armonk, NY).

Results

The overall 11,931 patients study population included 4,377 patients with DM (36.7%), and these exhibited significantly different patient and coronary artery disease characteristics compared with their no-DM counterparts (Supplemental Table 1). Briefly, patients with DM were more frequently female, more obese, and had more comorbidities.

A substantial 43.2% of study patients (n = 5,149) received multiple arterial bypass grafts (two arteries, n = 3,678 [30.9%]; three arteries, n = 1,471 [12.3%]) compared with 56.8% receiving conventional LITA-LAD (one artery, n = 6,782). Radial artery (RA) conduits were the primary second arterial conduit, at 94%, compared with only 6% right internal thoracic artery. Approximately 1% of patients overall received both bilateral internal thoracic arteries (BITA) and RA grafts. Patient risk factors and operative variables were substantially different across the three grafting groups for both DM and no-DM patients (Table 1; Supplemental Tables 2-4). Notably, multiarterial grafting strategies (two arteries or three arteries) were more frequently used in younger, male, larger body habitus, and healthier patients irrespective of diabetes status.

Effects of Arterial Grafting on Survival, All Patients

UNADJUSTED. Study patients were followed an average of 8.7 ± 4.4 years (maximum follow-up 15.5). In all, 3,780 overall deaths (31.7%) were documented and were more frequent among patients with diabetes (DM versus no-DM, 1,623 of 4,377 [37.1%] versus 2,157 of 7,554 [28.6%], p < 0.001). Consequently, the overall unadjusted 5-year survival (84.2% versus 88.5%), 10-year survival (62.9% versus 73.8%), and 15-year survival (42.4% versus 57.4%) rates were significantly worse for DM compared with no-DM patients (p < 0.001; Fig 1, left). The unadjusted 15-year survival, overall or irrespective of DM status, was systematically better with increasing number of arterial grafts (one artery versus two arteries versus three arteries, all p < 0.001; Fig 1, right).

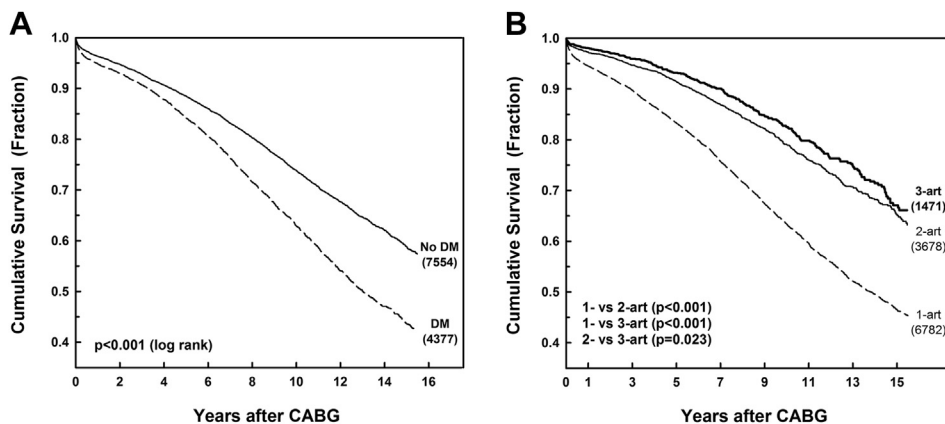
Multiarterial grafting was equally frequent in the DM and no-DM subgroups (1,856 of 4,377 [43.7%] versus 3,293 of 7,554 [42.4%], p = 0.21), as was the incidence of triple arterial grafting (three or more arteries DM versus no-DM, 517 [11.8%] versus 954 [12.6%], p = 0.20). Overall observed mortality was generally less with increasing number of arterial grafts for both the DM subcohort (one

artery, 1,165 of 2,521 [46.2%]; two arteries, 345 of 1,339 [25.8%]; and three arteries, 113 of 517 [21.9%], all p < 0.001) and the no-DM subcohort (one artery, 1,611 of 4,261 [37.8%]; two arteries, 398 of 2,339 [17.0%]; and three arteries, 148 of 954 [15.5%], all p < 0.001; Supplemental Fig 1). Figure 2 (left) shows separately for DM and no-DM patients the pairwise unadjusted survival comparisons for two arteries versus one artery (all p < 0.001; Fig 2A), three arteries versus one artery (p < 0.001; Fig 2B), and three arteries versus two arteries (not significant; Fig 2C).

RISK ADJUSTED. Comprehensive risk adjustment was first obtained in the overall 11,931 patient population by Cox regression analysis of 15-year mortality data involving a large number of patient factors, including diabetes status and increasing levels of arterial grafting. Decreased mortality was associated with increasing the number of arterial grafts (two arteries versus one artery [reference category], adjusted HR 0.87, 95% CI: 0.80 to 0.95, p = 0.002) and three arteries versus one artery (HR 0.83, 95% CI: 0.72 to 0.95, p = 0.005). Diabetes was also associated with a substantial adverse effect on late survival, with HR 1.43 (95% CI: 1.34 to 1.53, p < 0.001). Importantly, results of pairwise covariate adjusted comparisons of two arteries versus one artery, three arteries versus one artery, and three arteries versus two arteries in DM and no-DM-patients combined (Fig 3, left) were consistent and of comparable effect magnitudes.

The potential for diabetes and arterial grafting interaction confounding these risk-adjustment estimates of the effects of grafting strategy on late survival was next investigated by a similar comprehensive covariate adjustment approach but repeated separately for DM patients and no-DM patients. These results are summarized in Figure 3 (left). This stratified analysis showed that that a second (HR 0.84, 95% CI: 0.74 to 0.96) and third (HR 0.84, 95% CI: 0.67 to 1.04) arterial graft will confer a similar and appreciable survival benefit in no-DM patients.

Fig 1. Comparison of unadjusted 15-year Kaplan-Meier survival estimates (A) for diabetes mellitus (DM) patients (broken line) versus no-diabetes patients (solid line), and (B) for different arterial grafting subcohorts: one artery (1-art [broken line]), two arteries (2-art [light solid line]), and three arteries (3-art [heavy solid line]). (CABG = coronary artery bypass graft surgery.)



		Year of Follow-up							
AtRisk		1	3	5	7	9	11	13	15
No DM		7206	6681	6066	5062	3899	2722	1789	999
DM		4076	3710	3249	2521	1773	1143	683	343

		Year of Follow-up							
AtRisk		1	3	5	7	9	11	13	15
3-art		1409	1246	1097	992	687	519	307	151
2-art		3496	3232	2935	2289	1665	1042	636	261
1-art		6317	5918	5290	4380	3317	2325	1540	937

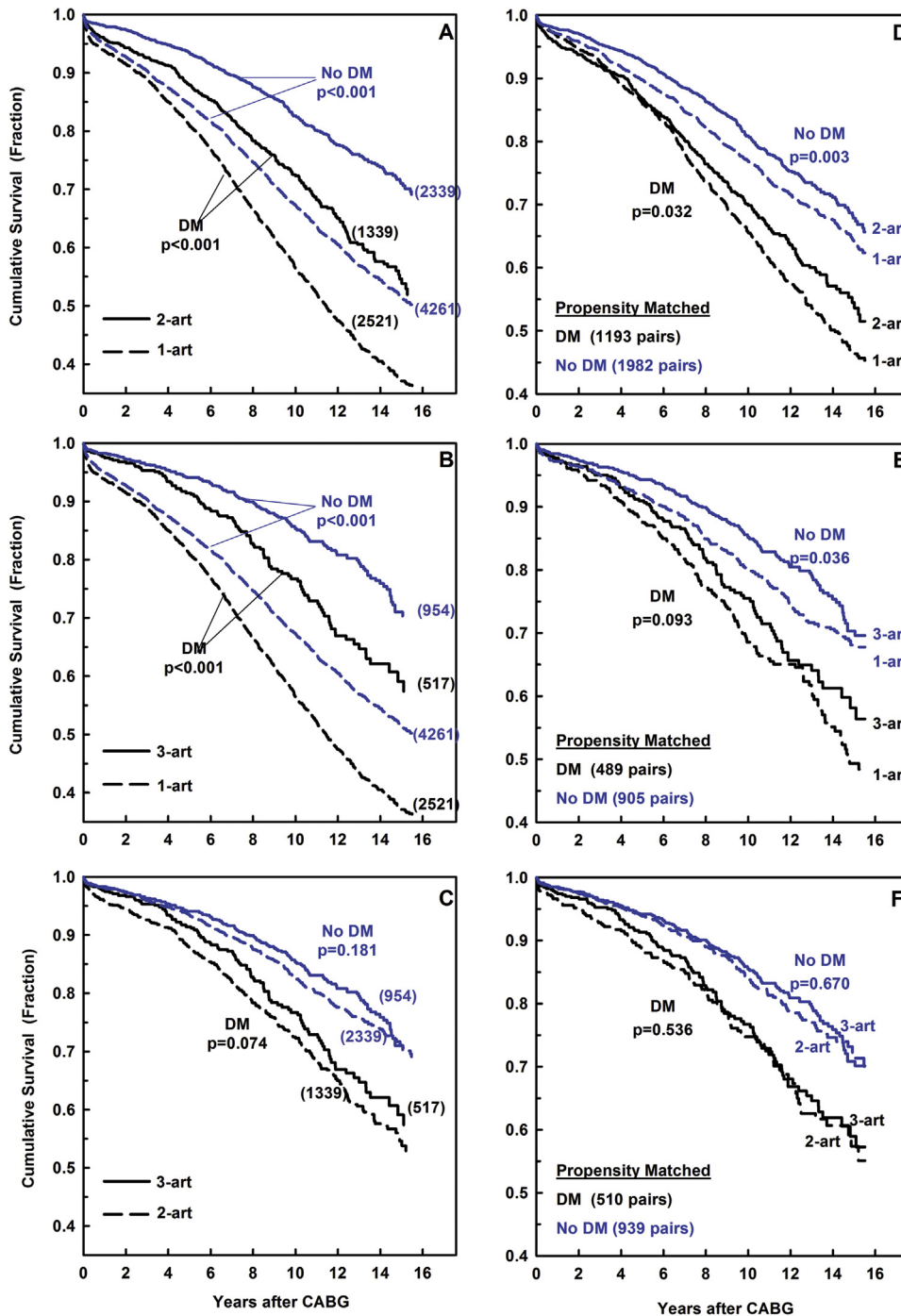


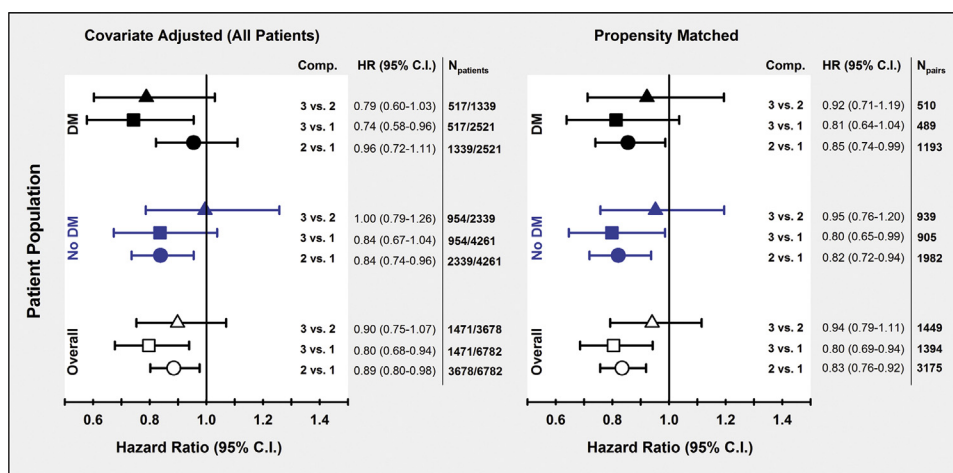
Fig 2. Pairwise comparisons of unadjusted 15-year Kaplan-Meier survival, estimated separately for diabetes mellitus (DM) patients (all black lines) versus no-diabetes (no-DM) patients (all blue lines) in arterial grafting subcohorts: (A, D) two arteries (2-art [solid lines]) versus one artery (1-art [broken lines]); (B, E) three arteries (3-art [solid lines]) versus one artery (broken lines); and (C, F) three arteries (solid lines) versus two arteries (broken lines). Left panels (A–C) represent all patients; right panels (D–F) represent propensity matched subgroups. (CABG = coronary artery bypass graft surgery.)

Alternatively, in patients with DM, the benefit from the second arterial graft was a modest one, but there is a substantial incremental benefit from a third arterial graft or more when compared with a single arterial graft approach (three arteries versus one artery, HR 0.74, 95% CI: 0.68 to 0.96), a trend that did not reach statistical significance when compared with a two-artery grafting strategy (three arteries versus two arteries, HR 0.79, 95% CI: 0.60 to 1.03).

Propensity Matched Analysis

A sensitivity analysis was done using propensity matched subcohorts to test the robustness of the above overall and diabetes status stratified risk-adjusted results quantifying the incremental benefits of additional arterial. Propensity score matching in DM patients yielded 1,193 pairs for two arteries versus one artery, 489 pairs for three arteries versus one artery, and 510 pairs for three arteries versus

Fig 3. Forest plots showing 15-year mortality hazard ratio (HR) with 95% confidence interval (C.I.) for pairwise arterial grafting group comparisons (Comp.): two arteries (2-art) versus (vs.) one artery (1-art); three arteries (3-art) versus one artery. (Left) Results from analysis of all patients using covariate-adjusted Cox regression, and (right) results from analysis of propensity matched patient subgroups. Analyses are shown for all patients, diabetes mellitus (DM) and no-DM combined (open symbols), and then separately for no-DM patients (blue symbols) and DM patients (solid symbols).



two arteries comparisons. The corresponding matching in no-DM patients yielded 1,982, 905, and 939 pairs, respectively. The two grafting method arms were always well matched with nonsignificant percent differences across all patient factors and for either DM or no-DM status (Supplemental Table 2). The results in the propensity matched groups were generally similar but not identical to our findings from the overall patient cohorts. Kaplan-Meier 15-year mortality after matching was significantly better for two-artery versus one-artery grafting (Fig 2D, Fig 3, right) for both DM (HR 0.85, 95% CI: 0.74 to 0.99, $p = 0.032$) and no-DM (HR 0.82, 95% CI: 0.72 to 0.94, $p = 0.003$). Use of three arteries compared with conventional one-artery CABG was also associated with significantly better Kaplan-Meier 15-year survival (Fig 2E, Fig 3, right) for no-DM patients (HR 0.80, 95% CI: 0.65 to 0.99, $p = 0.036$; Fig 3, right center) and a trend for better survival among DM patients (HR 0.81, 95% CI: 0.64 to 1.04, $p = 0.093$). Lastly, matched comparisons of three arteries versus two arteries exhibited essentially similar Kaplan-Meier 15-year survival (Fig 2F, Fig 3, right) for both DM patients (HR 0.92, 95% CI: 0.71 to 1.19, $p = 0.536$) and no-DM patients (HR 0.95, 95% CI: 0.76 to 1.20, $p = 0.670$).

Comment

Our results document that risk-adjusted (propensity score matched comparisons and comprehensive covariate adjusted comparisons) 15-year survival is enhanced by increasing the number of arterial grafts from the traditional one to two and to three or more arterial grafts, although the incremental survival benefit of a third arterial graft compared with two arterial grafts did not reach statistical significance. The three-artery versus one-artery survival benefit in LITA-based CABG is similar in magnitude in both the DM and no-DM subcohorts of CABG patients (Fig 3). As such, this study should serve as an additional impetus for increasing interest in utilizing extended multiarterial grafting.

Our results of improved long-term survival using two arterial grafts versus one arterial grafts, are not novel and confirm our reports [2, 3, 5] and those of others [1, 4, 6] in the overall CABG population as well in patients with diabetes [18, 19]. Importantly, two notable exceptions, with equivalent survival in prospective trials, have been recently published [20, 21]. Among our diabetes sub-cohort, the propensity matched analysis yielded a statistically significant survival advantage with two arterial grafts, whereas in the covariate adjusted analysis, we demonstrated only a statistically nonsignificant trend to improved survival. We have previously reported [5] improved long-term survival with multiarterial grafting among diabetes patients, which was largely driven by enhanced survival of noninsulin-dependent patients, with only a minimal impact among insulin-dependent patients. The insulin requirement is unknown in the New York database, and we were unable to control for this covariate in the present analysis, which may account for the discrepant findings.

The available literature on the value of three or more arterial grafts is limited. Guru and associates [16] using an administrative database found that two arterial grafts offered no survival advantage over single arterial grafting, although the follow-up period was only 5 years. When patients receiving either two or three arterial grafts were compared with single-artery patients, a statistically significant survival benefit was identified. The investigators were unable to determine the specific arterial grafts used in their analysis, given the limits of their administrative database.

The comparative outcomes of patients undergoing three-artery grafting versus two-artery grafting are less clear both in our analysis and in the literature in general. Comparing the long-term survival of patients receiving two arterial grafts versus three or more arterial grafts, we found a nonsignificant survival benefit of three or more arterial grafts in all CABG patients, the diabetes cohort and the nondiabetes cohorts (Fig 3). The nonsignificant results must be interpreted carefully considering the

limited number of three-artery patients available in this series, and additional studies will be required to more critically adjudicate the value of three arteries versus two arteries for CABG. The identified incremental survival benefit of three arteries versus two arteries, however, does seem to be more pronounced with diabetes. Guru and associates [16] also did not find a survival advantage associated with three-artery CABG and two-artery CABG.

Other small studies [9–17] also compared survival of patients receiving three arterial grafts versus two arterial grafts, with conflicting results. Mahommadi and colleagues [9] found no difference in long-term survival in BITA patients who received either an additional RA or venous grafts. Both Taggart and colleagues [10] and Grau and associates [17] noted an improved 5-year survival with BITA/RA grafting compared with BITA/SVG. Shi and associates [11] noted improved 15-year survival with three versus two arterial grafts. Conversely, Benedetto and associates [12] were unable to document improved survival in a group of low-risk BITA/SVG and BITA/RA patients. DiMauro and colleagues [15] were unable to document a survival difference with a third arterial graft (BITA/RA) compared with BITA/SVG. Use of SVG was associated with superior survival, however, when compared with the gastroepiploic artery as the third arterial graft, a result contradicted by Glineur and associates [13]. Others [14] found equivalent survival among patients with a three-artery (BITA and gastroepiploic artery) configuration compared with a BITA/SVG configuration. Importantly, in all these studies, the comparison groups were BITA based and therefore may not be comparable to our analysis based on an incremental number of RA grafts.

We hypothesize that the noted survival advantage associated with extended arterial grafting reflects the favorable arterial physiology resulting in decreased arterial graft atherosclerosis, less fibrointimal hyperplasia, intimal nitric oxide generation, and less size mismatch between arterial graft and coronary target, which together combine to enhance arterial graft durability [22]. Alternatively, arterial grafts have been associated with decreased downstream coronary atherosclerosis, which may also enhance patient survival [23].

The limitations of our study include its observational retrospective nature, which expose it to confounding by patient selection bias and inability to adjust for covariates that may not be included in the databases. Our databases lack appropriate granularity to ascertain the specific coronary targets to which the grafts were placed. In addition, because the databases were exclusively designed for 30-day perioperative outcome analysis, long-term important endpoints such as repeat revascularization rates, resource utilization, and reimaging rates were unavailable to us. Finally, we do not have data on graft patency, reintervention rates, or cause of death. Hence, the mortality rates in this study could have been only partly dependent on cardiac factors driven by graft occlusion. Although multiple risk adjustment techniques were utilized as confirmatory methods to eliminate bias, it

must be acknowledged that patient selection bias could not be entirely eliminated and that some of the survival benefit may be due to such bias rather than the intervention.

In conclusion, this is the first report documenting a survival advantage with extended arterial grafting with three or more arterial grafts using the RA in LITA-based CABG, and this survival benefit was independent of the patients' diabetes status. The incremental survival benefit of a third arterial graft compared with two arterial grafts was less prominent and only marginally significant among diabetes patients. Given our findings, we believe that multiarterial grafting remains an unexploited force multiplier that should be strongly considered by the heart team to improve long-term survival of all CABG patients, including those with diabetes.

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