A meta-analysis of adjusted hazard ratios from 20 observational studies of bilateral versus single internal thoracic artery coronary artery bypass grafting

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Objective: In 2001, a landmark meta-analysis of bilateral internal thoracic artery (BITA) versus single internal thoracic artery (SITA) coronary artery bypass grafting for long-term survival included 7 observational studies (only 3 of which reported adjusted hazard ratios [HRs]) enrolling approximately 16,000 patients. Updating the previous meta-analysis to determine whether BITA grafting reduces long-term mortality relative to SITA grafting, we exclusively abstracted, then combined in a meta-analysis, adjusted (not unadjusted) HRs from observational studies.

Methods: MEDLINE and EMBASE were searched until September 2013. Eligible studies were observational studies of BITA versus SITA grafting and reporting an adjusted HR for long-term (≥ 4 years) mortality as an outcome. Meta-regression analyses were performed to determine whether the effects of BITA grafting were modulated by the prespecified factors.

Results: Twenty observational studies enrolling 70,897 patients were identified and included. A pooled analysis suggested a significant reduction in long-term mortality with BITA relative to SITA grafting (HR, 0.80; 95% confidence interval, 0.77 to 0.84). When data from 6 pedicled and 6 skeletonized internal thoracic artery studies were separately pooled, BITA grafting was associated with a statistically significant 26% and 16% reduction in mortality relative to SITA grafting, respectively (P for subgroup differences = .04). A meta-regression coefficient was significantly negative for the proportion of men (-0.00960 ; -0.01806 to -0.00114).

Conclusions: Based on an updated meta-analysis of exclusive adjusted HRs from 20 observational studies enrolling more than 70,000 patients, BITA grafting seems to significantly reduce long-term mortality. As the proportion of men increases, BITA grafting is more beneficial in reducing mortality. (*J Thorac Cardiovasc Surg* 2014;148:1282-90)

In 2001, a landmark meta-analysis by Taggart and colleagues¹ of bilateral internal thoracic artery (BITA) versus single internal thoracic artery (SITA) grafting in coronary artery bypass grafting (CABG) was published in the *Lancet*. The BITA group had significantly better long-term survival than the SITA group (hazard ratio [HR] for death, 0.81; 95% confidence interval [CI], 0.70 to 0.94). The meta-analysis,¹ however, included only 7 observational studies²⁻⁸ that had enrolled 15,962 patients and were published in the 1990s. On the one hand, the Cox model was used in an attempt to adjust for the characteristics of the patients (eg, mean age, sex distribution, ventricular function, diabetic status, and so forth) that differed between the 2 groups in

3 reports^{3,5,8}; on the other hand, no statistical attempts to adjust for the distribution of these variables were made in the other studies.^{2,4,6,7} Furthermore, the largest (enrolling 10,124 patients) study by Lytle and colleagues⁵ had the highest weight (40.4%) in the meta-analysis,¹ and we revealed that exclusion of that study⁵ from the analysis substantially altered the overall result (statistically significant benefit in the BITA group than the SITA group for long-term mortality) to no statistically significant difference (HR, 0.85; 95% CI, 0.68 to 1.05; calculated by us) between the 2 groups. Since the previous meta-analysis¹ was performed, several studies on BITA versus SITA grafting in CABG have been published. In a recent large study published in 2013 by Parsa and colleagues,⁹ which enrolled 17,609 patients (more than the 15,962 patients included in the meta-analysis¹), adjusted mortality was similar (HR, 0.95; 95% CI, 0.83 to 1.08) between the BITA and SITA groups. To the best of our knowledge, only 2 randomized controlled trials^{10,11} of BITA versus SITA grafting in CABG have been published until now. In a small trial by Myers and colleagues,¹⁰ randomizing only 162 patients with a median 7.5-year follow-up, 5-year survival was not different (96.3% [95% CI, 92.0% to 98.7%] vs 93.8%

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Abbreviations and Acronyms

BITA	= bilateral internal thoracic artery
CABG	= coronary artery bypass grafting
CI	= confidence interval
ITA	= internal thoracic artery
OR	= odds ratio
RR	= relative risk
SITA	= single internal thoracic artery
SWI	= sternal wound infection

[95% CI, 88.4% to 97.3%]; $P = .39$) between the BITA and SITA groups. Another relatively large trial randomizing 3102 patients, the Arterial Revascularization Trial,¹¹ also demonstrated similar mortality at only 1 year (2.5% for BITA vs 2.3% for SITA; relative risk [RR], 1.06; 95% CI, 0.68 to 1.67). Accordingly, evidence for long-term survival in BITA versus SITA grafting in CABG from randomized controlled trials remains insufficient.

Updating the meta-analysis by Taggart and colleagues¹ to determine whether BITA grafting reduces long-term mortality relative to SITA grafting in CABG, we exclusively abstracted, then combined in a meta-analysis, adjusted (not unadjusted [crude]) risk estimates for long-term mortality from 20 observational studies (more than 70,000 patients were enrolled, which was more than quadruple the number of patients included in the previous meta-analysis¹). Moreover, meta-regression analyses were performed to determine whether the effects of BITA grafting were modulated by prespecified factors.

METHODS

Search Strategy and Study Selection

All observational studies of BITA versus SITA grafting that enrolled patients undergoing isolated CABG and reported adjusted risk estimates for long-term mortality were identified using the same search strategy as in the previous meta-analysis by Taggart and colleagues.¹ The MEDLINE and EMBASE databases were searched for publications containing the words “internal,” “mammary,” “thoracic,” “single,” “unilateral,” “bilateral,” “multiple,” “artery,” “arteries,” “singly” and in combination, between 1972 (MEDLINE) or 1980 (EMBASE) and September 2013. Two of us (H.T. and S.G.) independently inspected the electronic reports identified by the searches. We included published studies that had at least 100 patients in each group, and had a median (or mean) follow-up of at least 4 years. Only data from the last publication of centers that had produced sequential reports were included. We inspected the references of all studies to identify further studies.

Data Abstraction and Statistical Analysis

Data regarding detailed inclusion criteria, duration of follow-up, and all-cause long-term mortality (adjusted HRs for BITA vs SITA grafting and 95% CIs) were abstracted from each individual study. All study-specific estimates were combined using inverse variance-weighted averages of log-arithmic HRs in both fixed- and random-effects models (primary meta-analysis). Between-study heterogeneity was analyzed by means of standard χ^2 tests. Where nonsignificant statistical heterogeneity was identified, the

fixed-effects estimate was used preferentially as the summary measure. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual studies 1 at a time and recalculating the pooled HR estimates for the remaining studies (1-study-removed meta-analysis). To assess the impact of differential internal thoracic artery (ITA) harvesting techniques among the studies on the pooled estimate, the effects of BITA grafting on long-term mortality were explored separately in studies using the pedicled and skeletonized ITA. Publication bias was assessed graphically using a funnel plot and mathematically using adjusted rank correlation and linear regression tests. Mixed-effects (unrestricted maximum likelihood) meta-regression analyses were performed to determine whether the effects of BITA grafting were modulated by prespecified factors: that is, the mean length of follow-up or age (years), and proportion of men or diabetes (%). Meta-regression graphs depict the effect of BITA grafting on the outcome (plotted as logHR on the y-axis) as a function of a given factor (plotted as a mean or proportion of that factor on the x-axis). Meta-regression coefficients (slopes of the meta-regression line) show the estimated increase in logHR per unit increase in the covariate. Because logHR >0 corresponds to HR >1 and log HR <0 corresponds to HR <1, a negative coefficient indicates that as a given factor increases, the HR decreases; that is, BITA grafting is more beneficial in reducing the outcome of interest. All analyses were conducted using Review Manager version 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

RESULTS

Search Results

Our comprehensive search identified 20 observational studies^{3,8,9,12-28} of BITA versus SITA grafting that enrolled patients undergoing CABG and reported adjusted risk estimates for long-term mortality. In total, our meta-analysis included data on 70,897 patients undergoing CABG assigned to BITA or SITA grafting. The baseline characteristics for the patients enrolled in each study are summarized in Table 1. The most notable difference in some studies^{13,19,28} from the others was the criteria for enrollment of patients. The studies by Bonacchi and colleagues,¹³ Di Mauro and colleagues,¹⁵ Joo and colleagues,¹⁹ Kinoshita and colleagues,²¹ Navia and colleagues,²⁵ and Toumpoulis and colleagues²⁸ exclusively enrolled patients undergoing nonelective CABG,¹³ those aged less than 70 years,¹⁵ those undergoing off-pump CABG,¹⁹ those aged more than 70 years,²¹ those undergoing total arterial off-pump CABG,²⁵ and those with diabetes,²⁸ respectively. Despite the noted heterogeneity in design among studies, there was sufficient similarity between the populations and the hypotheses to merit inclusion of all 20 studies in the quantitative meta-analysis. The most dissimilar studies (Bonacchi and colleagues, 2006,¹³ Di Mauro and colleagues, 2005,¹⁵ Joo and colleagues, 2012,¹⁹ Kinoshita and colleagues, 2012,²¹ Navia and colleagues, 2013,²⁵ and Toumpoulis and colleagues, 2006²⁸) were sequentially eliminated in sensitivity analyses to assess their impact on the pooled effect estimate.

Primary Meta-Analysis

A pooled analysis of all 20 studies demonstrated a statistically significant 20% reduction in long-term mortality

TABLE 1. Trial design and patient characteristics

Study			Criteria		ITA harvesting	Adjustment method	Subgroup
First author, year	Institute	Period	Inclusion	Exclusion			
APPROACH (Kieser), 2011 ¹²	[The Province of Alberta, Canada]	April 1995 to March 2008	Isolated primary CABG	Non-Alberta residents	NA	MCPHR	
Bonacchi, 2006 ¹³	University of Florence	1997-2003	Nonelective CABG for unstable angina	—	Skeletonized	MCPHR	
Buxton, 1998 ³	Austin and Repatriation Medical Centre	1985-1995	[Including urgent/emergency CABG]	Severe or poorly controlled type 1 diabetes, morbid obesity, severe COAD, and cardiogenic shock for BITA	Pedicled	MCPHR	
Carrier, 2009 ¹⁴	Montreal Heart Institute	1995-2007	Isolated primary CABG	Redo CABG	Pedicled	MCPHR	Without statin
Di Mauro, 2005 ¹⁵	"G. D'Annunzio" University; University Hospital, Torino	September 1986 to December 1999	Primary CABG; <70 years	—	Pedicled skeletonized	MCPHR in PS-matched patients	With statin
Endo, 2001 ¹⁶	Tokyo Women's Medical University	April 1985 to March 1998	Elective, isolated primary CABG [including children with Kawasaki disease]	Long-term dialysis	Skeletonized	MCPHR	
Glineur, 2012 ¹⁷	Université Catholique de Louvain	July 1985 to November 1995	Isolated CABG	—	NA	MCPHR using PS strata	
Grau, 2012 ¹⁸	Valley Heart and Vascular Institute	1994-2010	Isolated CABG	Redo CABG; using RA	Routinely pedicled	MCPHR in PS-matched patients	
Joo, 2012 ¹⁹	Yonsei Cardiovascular Hospital	2000-2009	Isolated OPCAB	—	Semiskeltonized	PS matching	
Kelly, 2012 ²⁰	Queen Elizabeth II Health Sciences Center	1995-2009	Isolated primary CABG	Redo CABG	Pedicled	Nonparsimonious CPHR including PS quintiles	
Kinoshita, 2012 ²¹	Shiga University of Medical Science	2002-2010	Isolated CABG; >70 years	Emergency CABG with PCBS	Skeletonized	MCPHR in PS-matched patients	
Kurlansky, 2010 ²²	Florida Heart Research Institute	February 1972 to May 1994	Isolated CABG	—	Skeletonized	MCPHR	
Locker, 2012 ²³	Mayo Clinic	1993-2009	Isolated primary CABG	—	Pedicled skeletonized	Stepwise MCPHR	BITA only* BITA/RA BITA/SV
Lytte, 2004 ²⁴	Cleveland Clinic Foundation	1971-1989	Nonforeign; nonemergency, isolated primary CABG	Using non-ITA arterial grafts	NA	PS matching	
Navia, 2013 ²⁵	Institute Cardiovascular of Buenos Aires	January 2003 to May 2011	Urgent/elective total arterial OPCAB with LITA and RITA or RA	—	Mostly skeletonized	PS matching	
Parsa, 2013 ⁹	Duke University Medical Center	1984-2009	Isolated CABG	—	NA	MCPHR	
Pick, 1997 ⁸	Mayo Clinic	January 1984 to May 1986	Isolated CABG	Redo CABG; alternate venous or arterial conduits; multiple endarterectomies	Pedicled	MCPHR	
Puskas, 2012 ²⁶	Emory University	2002-2010	Isolated primary CABG	Emergency CABG	Pedicled/skeletonized	MCPHR using PS	
Stevens, 2004 ²⁷	Montreal Heart Institute	1985-1995	Isolated primary CABG with ≥3 grafts	Redo CABG; using RGEA	Pedicled	Stepwise MCPHR including PS	
Toumpoulis, 2006 ²⁸	St. Luke's-Roosevelt Hospital Center and Columbia University	January 1992 to March 2002	Diabetes; isolated CABG	—	NA	Backward stepwise MCPHR in PS-matched patients	
Total							

APPROACH, Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease database; ITA, internal thoracic artery; BITA, bilateral internal thoracic artery; SITA, single internal thoracic artery; SD, standard deviation; CABG, coronary artery bypass grafting; NA, not available; MCPHR, multivariable Cox proportional hazards regression; EF, ejection fraction; COAD, chronic-obstructive-airway disease; PS, propensity score; RA, radial artery; OPCAB, off-pump coronary artery bypass; CPHR, Cox proportional hazards regression; SV, saphenous vein; LITA, left internal thoracic artery; RITA, right internal thoracic artery; PCBS, percutaneous cardiopulmonary bypass support; LVD, left ventricular dysfunction; RGEA, right gastroepiploic artery. *Composite-T grafting. †Including other multiple arterial grafting (n = 180).

with BITA relative to SITA grafting in the fixed-effects model (HR, 0.80; 95% CI, 0.77 to 0.84; $P < .00001$; Figure 1). There was minimal study heterogeneity of the

results ($P = .30$) and, accordingly, little difference in the pooled result from random-effects modeling (HR, 0.80; 95% CI, 0.76 to 0.84; $P < .00001$).

TABLE 1. Continued

Number of patients		Mean (±SD) length of follow-up (years)		Mean (±SD) age (years)		Men (%)		Ventricular function				Diabetes (%)	
BITA	SITA	BITA	SITA	BITA	SITA	BITA	SITA	Classification	BITA	SITA	BITA	SITA	
1038	4029	6.4 ± 3.2	7.1 ± 3.4	58.0 ± 9.1	67.6 ± 9.5	NA		EF	<0.20 0.20-0.34 0.35-0.50 >0.50	0.4% 3.4% 20.5% 71.0%	0.4% 5.4% 22.2% 66.5%	27.8	26.2
320	332	5.6 ± 1.4		59 ± 14	63 ± 11	81.9	80.1	EF	<0.35	19.1%	20.8%	30.0	33.7
1269	1557	4.3		58.6 ± 9	64.9 ± 9	89.4	78.0	EF	<0.50	4.9%	24.2%	6.8	19.9
69	585	6		61 ± 9	68 ± 8	83.9	70.9			NA		20.6	31.3
1166	4835												
476	476	8.6 ± 4.8	8.8 ± 4.0	59.1 ± 7.6	58.8 ± 8.1	81.7	85.5	EF	0.597 ± 0.128	0.600 ± 0.136		23.3	22.3
443	688	Median, 6.15		Median, 61	Median, 62	90.3	80.8	EF	Median, 0.54	Median, 0.54		42.9	40.3
297	291	16.3 ± 5.4	15.1 ± 6.3	57 ± 9	61 ± 10	92.6	89.0	EF	0.56 ± 0.13	0.53 ± 0.14		16.2	27.8
928	928	9.0 ± 5		60.9 ± 9	62.1 ± 9	89.2	89.3	EF	0.52 ± 0.11	0.51 ± 0.12		10.8	10.9
366	366	7.00 ± 2.09	7.10 ± 2.70	60.73 ± 8.14	60.14 ± 8.6	76.2	78.7	EF	0.569 ± 0.128	0.559 ± 0.137		52.5	53.3
1079	6554	Median, 5.4	Median, 4.6	58.4 ± 10.0	65.0 ± 10.1	82.0	75.4	EF	<0.40	7.2%	11.9%	25.6	37.4
217	217	4.3 ± 1.6		76.1 ± 3.6	76.3 ± 4.8	78.3	76.5	EF	0.53 ± 0.17	0.52 ± 0.16		55.8	51.2
2215	2369	12.7	11.1	62.9 ± 10.0	67.5 ± 9.4	85.1	74.3	EF	<0.30 0.30-0.50 >0.50	3.9% 27.1% 68.2%	6.2% 27.7% 64.9%	20.8	27.3
271	7435	7.6 ± 4.6†		58 ± 9†	68 ± 9	84.9†	75.2	EF	0.57 ± 0.11†	0.55 ± 0.14		33.5†	18.1
147													
589													
1152	1152	16.2 ± 2.4	16.3 ± 2.5	57.5 ± 8.1	57.8 ± 8.3	88	86	LVD	Severe Moderate Mild Normal/none	24.0% 14.0% 26.6% 35.4%	23.4% 13.1% 26.6% 36.9%	11.9	12.2
149	149	3.5	5.7	68 ± 8.4	67 ± 9.6	82.5	81.2	EF	<0.35	30.2%	30.2%	30.8	32.2
728	16,881	NA [25-year mortality curves available]		Median, 59	Median, 64	80.2	71.5	EF		Median, 0.51	Median, 0.52	14.7	19.9
160	161	9.8 ± 2.8		60	62	82	80	EF		Mean, 0.58	Mean, 0.57	17.5	27
812	2715	NA [8-year survival curves available]		58.4 ± 10.1	63.9 ± 10.8	84.0	67.0	EF		0.517 ± 0.112	0.497 ± 0.128	28.6	44.7
1808	2498	8 ± 2	12 ± 3	57 ± 9	63 ± 9	88.5	74.9			NA		11.8	16.8
490	490	4.7 ± 3.0		63.6 ± 9.9	64.5 ± 9.4	55.1	56.1	EF	<0.30 0.30-0.50 >0.50	79.4% 43.7% 76.9%	80.8% 38.6% 80.6%	100	
16189	54708												

Sensitivity Analyses

To assess the impact of qualitative heterogeneity in the study design and patient selection on the pooled effect

estimate, we performed several sensitivity analyses. First, we sequentially excluded Bonacchi and colleagues, 2006,¹³ Di Mauro and colleagues, 2005,¹⁵ Kinoshita and

FIGURE 1. Forest plot of adjusted hazard ratios for long-term mortality among patients assigned to bilateral versus single internal thoracic artery grafting. BITA, Bilateral internal thoracic artery; SITA, single internal thoracic artery grafting; SE, standard error; CI, confidence interval; IV, inverse variance; RA, radial artery; SV, saphenous vein.

colleagues, 2012,²¹ and Toumpoulis and colleagues, 2006,²⁸ which exclusively enrolled patients undergoing nonelective CABG for unstable angina,¹³ those aged less than 70 years,¹⁵ those aged more than 70 years,²¹ and those with diabetes,²⁸ respectively; combining the remaining 19 studies still generated a statistically significant result favoring BITA grafting (fixed-effects HR for exclusion of Bonacchi and colleagues, 2006,¹³ 0.81; 95% CI, 0.77 to 0.84; $P < .00001$; fixed-effects HR for exclusion of Di Mauro and colleagues, 2005,¹⁵ 0.81; 95% CI, 0.77 to 0.84; $P < .00001$; fixed-effects HR for exclusion of Kinoshita and colleagues, 2012,²¹ 0.81; 95% CI, 0.77 to 0.84; $P < .00001$; fixed-effects HR for exclusion of Toumpoulis and colleagues, 2006,²⁸ 0.80; 95% CI, 0.77 to 0.84; $P < .00001$). Second, we excluded both Joo and colleagues, 2012¹⁹ and Navia and colleagues, 2013,²⁵ both of which exclusively enrolled patients undergoing off-pump CABG.^{19,25} Without them, there was still a statistically significant benefit for BITA grafting in pooled analysis of the remaining 18 studies (fixed-effects HR, 0.80; 95% CI, 0.77 to 0.84; $P < .00001$). In general, exclusion of any single study from the analysis did not substantively alter the overall result of our analysis (1-study-removed meta-analysis; Figure 2). When data from 6 pedicled^{3,8,14,18,20,27} (enrolling 23,597 patients) and 6 skeletonized ITA studies^{13,16,19,21,22,25} (enrolling 7,831 patients) were separately pooled using the fixed-effects model, BITA

grafting was associated with a statistically significant 26% (HR, 0.74; 95% CI, 0.68 to 0.81; P for effect $< .00001$; P for heterogeneity = .51) and 16% (HR, 0.84; 95% CI, 0.78 to 0.91; P for effect $< .0001$; P for heterogeneity = .65) reduction in long-term mortality relative to SITA grafting (P for subgroup differences = .04; Figure 3).

Publication Bias

To assess publication bias we generated a funnel plot of the logarithm of effect size versus the precision (reciprocal of the standard error) for each study (data not shown). There was no evidence of significant publication bias (2-tailed P with continuity correction = .95787 by the adjusted rank correlation test and 2-tailed $P = .21818$ by the linear regression test).

Meta-Regression Analyses

Meta-regression coefficients were not statistically significant for the mean length of follow-up (coefficient, -0.00194; 95% CI, -0.01526 to 0.01137; $P = .77472$), mean age (coefficient, 0.01087; 95% CI, -0.00448 to 0.02622; $P = .16528$), and proportion of diabetes (coefficient, -0.00167; 95% CI, -0.00137 to 0.00471; $P = .28178$). However, a meta-regression coefficient was significantly negative for the proportion of men (coefficient, -0.00960; 95% CI, -0.01806 to -0.00114; $P = .02621$; Figure 4),

FIGURE 2. One-study-removed meta-analysis of adjusted hazard ratios for long-term mortality among patients assigned to bilateral versus single internal thoracic artery grafting. CI, Confidence interval; BITA, bilateral internal thoracic artery; SITA, single internal thoracic artery grafting.

which would indicate that as the proportion of men increases, the HR decreases; that is, BITA grafting is more beneficial in reducing long-term mortality.

DISCUSSION
The results of our analysis suggest that BITA grafting may reduce long-term mortality by 20% relative to SITA

FIGURE 3. Forest plot of adjusted hazard ratios for long-term mortality among patients assigned to bilateral versus single internal thoracic artery grafting pooled separately in studies using the pedicled and skeletonized internal thoracic artery. BITA, Bilateral internal thoracic artery; SITA, single internal thoracic artery grafting; SE, standard error; IV, inverse variance; CI, confidence interval; ITA, internal thoracic artery.

FIGURE 4. Meta-regression of proportion of men (%) on logarithmic hazard ratio for long-term mortality among patients assigned to bilateral versus single internal thoracic artery grafting.

grafting in patients undergoing CABG, which is most compelling with adjusted data from 70,897 patients assigned in 20 different observational studies and robust in sensitivity analyses. Because the present meta-analysis overcomes the limitations of the analysis Taggart and colleagues¹ mentioned earlier, the results could provide better (not the best) evidence until a large randomized controlled trial reports long-term outcomes in the future.

In 1 of our sensitivity analyses, BITA grafting was associated with a 26% reduction in long-term mortality relative to SITA grafting in pedicled ITA studies, which was better (P for subgroup differences = .04) than a 16% reduction in skeletonized ITA studies. The 6 skeletonized ITA studies^{13,16,19,21,22,25} analyzed enrolled only one-third (approximately 8000 patients) of approximately 24,000 patients enrolled in the 6 pedicled ITA studies.^{3,8,14,18,20,27} Evidence is limited in terms of pedicled versus skeletonized ITA-graft patency.²⁹ Although theoretically skeletonization of the ITA might adversely affect its long-term resistance to atherosclerosis, the skeletonized ITA has not been used long enough to establish whether a decline in patency will occur after several years.³⁰ In a recent systematic review, the follow-up data were not long-term; only 2 studies provided patency rates beyond 5 years.²⁹ Also, only 4 were comparative studies of skeletonized versus pedicled conduits, in which skeletonization patency was at least comparable with pedicled conduits and in 2 studies even higher.²⁹ Sternal wound infection (SWI), the most serious manifestation of which is mediastinitis, is recognized as an important complication of CABG, and mediastinitis can be severe and potentially lethal. Skeletonized ITA grafting seems to reduce the incidence of postoperative SWI in comparison with pedicled ITA grafting after CABG. A recent meta-analysis³¹ of 22 studies (involving 4817 patients) showed a statistically significant difference in

favor of skeletonized ITA grafting (odds ratio [OR], 0.443; 95% CI, 0.323 to 0.608, $P < .001$), which was also observed in subgroups of BITA grafting (OR, 0.381; 95% CI, 0.257 to 0.565; $P < .001$) and diabetic patients with BITA grafting (OR, 0.188; 95% CI, 0.098 to 0.360; $P < .001$). To confirm the long-term survival benefit of BITA grafting in pedicled versus skeletonized ITA studies suggested in our sensitivity analysis, further investigations are required.

One of our meta-regression analyses indicated that as the proportion of men increases, BITA grafting is more beneficial in reducing long-term mortality. A post hoc analysis³² of the same cohort (4584 patients) as the study by Kurlansky and colleagues²² (included in the present meta-analysis) may support our result. In multivariable Cox proportional hazard regression analyses for unmatched patients, the choice of the BITA conduit was identified as a predictor of late survival among men (HR, 0.8; 95% CI, 0.7 to 0.9; $P < .001$) but not associated with late survival among women.³² In the propensity score matched male groups, the median survival for SITA patients was 14.2 years (95% CI, 13.2 to 15.2) compared with 15.8 years (95% CI, 15.0 to 16.8) for BITA patients. The equality of the survival distribution for these 2 groups of male patients demonstrated a significant difference ($P < .001$).³² These results provide further evidence of the survival benefits achieved in male patients with BITA grafting. In the propensity score matched female groups, however, the median survival for SITA patients was 14.0 years (95% CI, 12.8 to 15.4) and that for BITA patients was 13.7 years (95% CI, 12.8 to 14.7), with no significant difference in survival distribution ($P = .571$).³² Therefore, BITA grafting seems to confer an incremental survival benefit relative to SITA grafting in men but not in women. Although these results represent the largest experience in the current literature that specifically addresses long-term survival of BITA grafting in women, it may be that 329 patients, compared with the male cohorts of more than 1000 patients, is just not sufficient to demonstrate a survival advantage (type II error).³²

As an important point of concern, SWI is one of the main reasons limiting the extensive use of more than 1 ITA. A recent meta-analysis³³ of 32 studies (consisting of 172,880 patients) showed that BITA grafting increases the risk of SWI compared with SITA grafting. The risk of SWI in the BITA group was higher (RR for SITA vs BITA, 0.62; 95% CI, 0.55 to 0.71) than that in the SITA group. This adverse effect further extends to diabetic and elderly patients³³; BITA grafting was also associated with a higher risk of SWI in diabetic patients (RR for SITA vs BITA, 0.65; 95% CI, 0.52 to 0.81; 12 studies consisting of 128,109 patients) as well as elderly patients (RR for SITA vs BITA, 0.45; 95% CI, 0.33 to 0.62; 5 studies consisting of 8206 patients). Also in another recent meta-analysis³⁴ of 1 randomized controlled trial and 10 observational

studies (enrolling 126,235 diabetic patients), deep SWI occurred in 3.1% and 1.6% for the BITA and LITA cohorts, respectively (RR, 1.71; 95% CI, 1.37 to 2.14). Despite the higher risk of SWI in BITA grafting, the present meta-analysis demonstrated the obvious benefit for BITA grafting for long-term survival.

Our analysis must be viewed in the context of its limitations. We used only data from observational studies, not randomized controlled trials. Although patients enrolled in randomized trials may not be representative of patients typically seen in clinical practice, this is the study design least vulnerable to bias because randomized trials balance both known and unknown confounders across treatment groups. Potential biases are likely to be greater for observational studies compared with randomized trials, however, so results should always be interpreted with caution when they are included in reviews and meta-analyses.³⁵ Particular concerns arise with respect to differences between patients in different intervention groups (selection bias). Unlike for randomized trials, it would usually be appropriate to analyze adjusted (rather than unadjusted) effect estimates, that is, analyses that attempt to control for confounding.³⁵ To reduce the effect of treatment selection bias and potential confounding in observational studies, rigorous adjustment for significant differences in the baseline characteristics of patients should be conducted. Furthermore, adjusted (not unadjusted) estimates ought to be pooled in a meta-analysis that includes observational studies. In the present meta-analysis, we strictly abstracted, then combined in a meta-analysis, exclusive adjusted (not unadjusted) risk estimates from observational studies. Meanwhile, our results may be influenced by a publication bias favoring BITA grafting. This risk was minimized through an exhaustive search of the available literature. Although the statistical tests did not indicate publication bias, there is clearly limited power to detect such bias, given the small number of studies examined.

Despite these acknowledged limitations, we found that, based on an updated meta-analysis of exclusive adjusted risk estimates from 20 observational studies enrolling more than 70,000 patients, BITA grafting is likely effective in the prevention of long-term mortality in patients undergoing CABG. Because mortality reduction must imply the greatest clinical benefit among patients undergoing CABG, BITA grafting should be considered for patients who meet the criteria for enrollment in the observational studies discussed earlier.

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