Is the era of bilateral internal thoracic artery grafting coming for diabetic patients? An updated meta-analysis

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ABSTRACT

Objective: Because of an increased risk of sternal wound complications, the use of bilateral internal thoracic artery grafting in diabetic patients remains controversial. The objective of the present meta-analysis is to compare the safety and efficacy of single internal thoracic artery and bilateral internal thoracic artery grafting in the diabetic population.

Methods: Four electronic databases, including PubMed, the Cochrane Library, Embase, and ISI Web of Knowledge, were comprehensively searched. Prospective randomized trials or observational studies comparing single internal thoracic artery and bilateral internal thoracic artery were considered eligible for the current study.

Results: A literature search yielded 1 randomized controlled trial and 17 observational studies (129,871 diabetic patients: 124,233 single internal thoracic arteries and 5638 bilateral internal thoracic arteries). Pooled analysis demonstrated overall incidence of deep sternal wound infection in the bilateral internal thoracic artery grafting group was significantly higher than in the single internal thoracic artery grafting group (3.26% for bilateral internal thoracic artery vs 1.70% for single internal thoracic artery). No significant difference was found between both groups in terms of risk of deep sternal wound infection when the skeletonized harvesting technique was adopted. Furthermore, in-hospital mortality was comparable between both groups (2.80% for bilateral internal thoracic artery vs 2.36% for single internal thoracic artery). However, compared with single internal thoracic artery grafting, bilateral internal thoracic artery grafting could confer a lower risk for long-term overall mortality (hazard ratio, 1.41; 95% confidence interval, 1.18-1.67; $P < .001$; $I^2 = 63\%$) and cardiac mortality (hazard ratio, 3.15; 95% confidence interval, 2.23-4.46; $P < .001$; $I^2 = 0\%$).

Conclusions: Compared with single internal thoracic artery grafting, bilateral internal thoracic artery grafting is associated with enhanced long-term survival among diabetic patients. Skeletonization of bilateral internal thoracic artery is not associated with an increased risk of deep sternal wound infection. Therefore, surgeons should be encouraged to adopt bilateral internal thoracic artery grafting in a skeletonized manner more routinely in diabetic patients. (*J Thorac Cardiovasc Surg* 2019;158:1559-70)

Aggregated overall Kaplan-Meier survival curves based on reconstructed and patient data.

Central Message

BITA grafting could increase long-term overall and cardiac mortality-free survival among the diabetic population.

Perspective

Because of an increased risk of sternal wound complications, the use of BITA grafting in diabetic patients remains controversial. This study suggests that for diabetic patients, BITA grafting could increase long-term overall and cardiac mortality-free survival, and skeletonization of BITA will not increase the risk of deep sternal wound infection.

See Commentaries on pages 1571 and 1573.

During the last decade, some studies and guidelines have supported the superiority of coronary artery bypass grafting (CABG) over percutaneous therapy for diabetic patients with multivessel disease.¹⁻³ Single internal thoracic artery

(SITA) has been regarded as an independent factor of improved survival for diabetic patients.⁴ However, bilateral internal thoracic artery (BITA) grafting is associated with improved survival and freedom from repeat revascularization

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Abbreviations and Acronyms

BITA	= bilateral internal thoracic artery
CABG	= coronary artery bypass grafting
CI	= confidence interval
DSWI	= deep sternal wound infection
HR	= hazard ratio
ITA	= internal thoracic artery
RR	= risk ratio
SITA	= single internal thoracic artery

Scanning this QR code will take you to the article title page to access supplementary information.

compared with SITA grafting in the general population.⁵ Unfortunately, despite the potential benefit of BITA grafting, the application of the BITA grafting technique in diabetic patients is controversial. The primary reason for avoiding the use of BITA is the increased risk of deep sternal wound infection (DSWI), which is particularly common among diabetic patients.⁶ BITA grafting with meticulous skeletonized technique of internal thoracic artery (ITA) harvesting is not associated with an increased risk of wound infection.⁷⁻⁹

A previous meta-analysis by Kajimoto and colleagues¹⁰ concluded that CABG using BITA grafts was an excellent strategy, even for diabetic patients. However, not all eligible studies, including some new observational studies, have been included in this meta-analysis. In addition, existing reviews, including a meta-analysis conducted by Deo,¹¹ mainly focused on the incidence of DSWI, without a thorough analysis of long-term survival. Thus, this updated meta-analysis was conducted to compare short-term and long-term clinical outcomes of bilateral versus SITA grafting in diabetic patients.

MATERIAL AND METHODS

Search Strategy

A literature search was carried out by using PubMed, the Cochrane Library, Embase, and ISI Web of Knowledge of all related studies published between 1966 and January 2018. The search terms (“internal mammary artery” OR “internal thoracic artery”) AND (“single” OR “unilateral”) AND (“bilateral” OR “double”) AND (“diabetes mellitus OR diabetics”) were entered as keywords and MeSH terms.

Eligibility Criteria

Trials were selected on the basis of the following inclusion criteria: (1) studies comparing SITA and BITA grafting for diabetic patients; (2) patients enrolled in studies underwent isolated CABG, either on pump or off pump; and (3) studies providing postoperative DSWI, early mortality, or Kaplan–Meier curve for long-term overall survival or cardiac mortality-free survival.

Study Selection

Two researchers (P.Z. and P.Z.) independently screened all studies for inclusion. In duplicate, title and abstracts were screened, and then potentially eligible records in full text were retrieved for inclusion. Disagreements were resolved by discussion and consensus. Agreement between researchers regarding study inclusion was assessed using the Cohen k statistic.

End Points and Their Definitions

In most of the included studies, diabetic patients were diagnosed with diabetes mellitus according to the International Classification of Diseases, 10th Revision, with insulin or oral treatment before operation. The end points of this study were as follows: (1) DSWI; (2) early mortality; (3) Kaplan–Meier curve for long-term overall survival; and (4) Kaplan–Meier curve for long-term cardiac mortality-free survival. According to the guidelines of the Centers for Disease Control and Prevention,¹² DSWI should consist of at least 1 of the following criteria: (1) isolation of an organism from culture of mediastinal tissue or fluid; (2) evidence of mediastinitis; and (3) chest instability or pain, sternal instability, or fever present in combination with purulent discharge from the mediastinum or an isolated organism from blood or tissue cultures. Early mortality included in-hospital or 30-day mortality. Long-term overall survival was defined as time from surgery to death from any causes. Long-term cardiac mortality-free survival was defined as time from surgery to death from cardiac-related events, including myocardial infarction, heart failure, and sudden death.

Data Extraction and Quality Assessment

Two researchers (P.Z. and P.Z.) independently extracted the following information from each study: lead author, publication year, participant characteristics, type of study, and number of grafts. Reviewers extracted the following outcomes: DSWI, early mortality, or Kaplan–Meier curves for long-term overall survival or cardiac mortality-free survival. Quality of included studies was assessed with the Newcastle–Ottawa scale for observational studies.

Statistical Analysis

This meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analysis guideline.¹³ For DSWI and early mortality, data regarding end points was used to generate risk ratios (RRs) and 95% confidence intervals (CIs). The I^2 -statistics were performed to test for heterogeneity between the included studies. Random-effect models were chosen over fixed-effect models because their assumptions accounted for the presences of variability among studies. Forest plots were then created for graphic presentation of clinical outcomes. To generate the pooled hazard ratio (HR) and 95% CI for long-term mortality, first, Kaplan–Meier curves for long-term overall and cardiac mortality-free survival in each included study was digitalized in Engauge digitizer software (version 10.4; maintained by Mark Mitchell). Second, log HR and corresponding standard error for each included study could be acquired with digitalized Kaplan–Meier curve data in the specific excel file provided by Tierney and colleagues.¹⁴ Finally, log HR and its corresponding standard error for each study could be combined in Review Manager (version 5.1.2; Cochrane Collaboration, Oxford, United Kingdom). With regard to aggregated Kaplan–Meier survival curves for long-term overall and cardiac mortality-free survival, digitalized Kaplan–Meier curve data, including Survival and NbRisk for each study, were aggregated to form combined survival curves in package MetaSurv of R software (version 3.4.3).

Subgroup analyses were performed for subsets of studies (propensity-matched cohorts and unmatched cohort) and for subsets of patients who underwent skeletonized ITA harvesting. Publication bias assessment was analyzed by funnel plots and evaluated by Egger's test and Begg's test. We assessed publication bias by examining funnel plots when the number of trials reporting the primary outcomes was 10 or more. Statistical analysis was conducted with Review Manager or R software.

TABLE 1. Main characteristics of included studies

Trials	Patients SITA/BITA (N)	Study period	Length of follow-up, mean, y	Skeletonized SITA/BITA (%)	Outcomes	DM SITA/BITA (%)	Study design
Endo 2003 ¹⁵	227/190	1985-1998	8.1*	100/100	DSWI, long-term all-cause death, long-term cardiac death	100/100	Retrospective
Hirofani 2003 ¹⁶	124/179	1991-2003	NA	0/0	DSWI, in-hospital mortality, long-term all-cause death, long-term cardiac death	100/100	Retrospective
Lev-Ran 2003 ¹⁷	74/50	1996-2001	4.6*	100/100	DSWI, 30-d mortality, long-term all-cause death, long-term cardiac death	100/100	Retrospective
Tavolacci 2003 ¹⁸	177/79	1998-2000	NA	NA	DSWI	100/100	Retrospective
Dorman 2004 ¹⁹	414/414	1972-1994	8.9	0/0	DSWI, 30-d mortality, long-term all-cause death	100/100	Propensity score matched
Lev-Ran 2004 ²⁰	57/228	1996-1998	5.0*	100/100	DSWI, 30-d mortality, long-term all-cause death, long-term cardiac death	100/100	Retrospective
Stevens 2004 ²¹	419/214	1985-1995	11.0	0/0	DSWI, 30-d mortality, in-hospital mortality, long-term all-cause death	100/100	Retrospective
Calafiore 2005 ⁹	200/200	1991-2001	6.0	84/85	DSWI, in-hospital mortality, long-term all-cause death, long-term cardiac death	100/100	Propensity score matched
Momin 2005 ²²	524/396	1992-2002	NA	0/0	DSWI, 30-d mortality	100/100	Retrospective
Toumpoulis 2006 ²³	490/490	1992-2002	4.7	NA	DSWI, 30-d mortality, in-hospital mortality, long-term all-cause death	100/100	Propensity score matched
Savage 2007 ²⁶	119,016/1732	2002-2004	NA	NA	DSWI, 30-d mortality	100/100	Retrospective
Agrifoglio 2008 ²⁷	41/40	2006	1.0	0/0	DSWI	100/100	Retrospective
Kinoshita 2010 ⁸	170/170	2002-2009	3.2	100/100	DSWI, 30-d mortality, long-term all-cause death, long-term cardiac death	100/100	Propensity score matched
Konstanty-Kalandyk 2012 ²⁴	109/38	2006-2008	0.25	0/0	DSWI, 30-d mortality	100/100	Retrospective
Gansera 2016 ²⁹	125/125	2000-2011	9.3	NA	DSWI, 30-d mortality	100/100	Propensity score matched
Puskas 2012 ²⁵	2715/812	2002-2010	NA	NA	DSWI, in-hospital death, long-term all-cause death	44.7/28.6	Retrospective
Taggart 2012 ²⁸	1554/1318	1996-2010	12.2	NA	DSWI	23.4/23.9	Randomized controlled trial
Pevni 2017 ⁷	490/490	2004-2007	1.0	100/100	DSWI, in-hospital death, long-term all-cause death	100/100	Propensity score matched

SITA, Single internal thoracic artery; BITA, bilateral internal thoracic artery; N, number of patients; DM, diabetes mellitus; DSWI, deep sternal wound infection; NA, not available.

*Length of follow-up, median, y.

RESULTS

Studies Retrieved and Characteristics

A brief description of the results in present study can be seen in [Video 1](#). A total of 323 potentially relevant studies were identified in the initial search ([Figure E1](#), Preferred

Reporting Items for Systematic Reviews and Meta-Analyses diagram [[Online Data Supplement 1](#)]). After review, 18 studies, including 1 randomized controlled trial and 17 observational studies,^{7-9,15-29} were eligible for inclusion ([Table 1](#)). The k statistic for the final process of

TABLE 2. Main characteristics of patients in included studies

Patient baseline	No. of studies reporting variables	Report No. of patients		OR/mean difference, 95% CI	P value
		SITA	BITA		
Mean age, y	14	121,940	4355	2.54 [0.98-4.10]	.001*
Female gender, N	15	122,167	4545	1.42 [1.14-1.77]	.002*
BMI, mean (SD)	7	119,991	2654	0.59 [0.16-1.02]	.007*
Preoperative characteristics					
COPD, N	9	121,043	3330	1.42 [1.22-1.65]	<.001*
HTN, N	8	2241	1812	1.13 [0.81-1.58]	.48
Renal impairment, N	8	120,868	3360	1.66 [1.18-2.33]	.004*
Prior CVD, N	7	1709	1656	1.46 [0.66-3.24]	.35
Prior MI, N	12	121,689	4226	1.08 [0.94-1.24]	.30
Intraoperative characteristics					
No. of grafts, mean (SD)	10	2057	1854	−0.22 [−0.35 to −0.08]	.002*
CPB, min	5	1076	1222	−8.43 [−22.37 to 5.50]	.24
Crossclamping time, min	6	819	949	−5.97 [−11.23 to −0.71]	.03*

OR, Odds ratio; CI, confidence interval; SITA, single internal thoracic artery; BITA, bilateral internal thoracic artery; N, number of patients; BMI, body mass index; SD, standard deviation; COPD, chronic obstructive pulmonary disease; HTN, hypertension; CVD, cerebrovascular disease; MI, myocardial infarction; CPB, cardiopulmonary bypass. *Statistically significant.

selection was 0.81. Of these, all 18 studies^{7-9,15-29} evaluated DSWI, 15 studies evaluated early mortality,^{7,15,17,19,26,29} 10 studies evaluated long-term overall survival,^{7,8,9,15,17,19,23,25} and 4 studies evaluated long-term cardiac mortality-free survival.^{8,9,17,20} Propensity score–matched analysis was reported in 7 studies.^{7-9,19,23,25,29} A skeletonized harvesting technique

of ITA was adopted in 5 studies.^{7,8,15,17,20} Patient baseline, preoperative, and intraoperative characteristics are shown in Table E1. Definition and perioperative management of diabetes mellitus for each study are shown in Table 3. All of the confounders used in propensity score analysis are presented in Table 4.

TABLE 3. Definition and perioperative management of diabetes mellitus

Study	Described definition of DM	Type of DM		Treatment of DM before OP		Postoperative glucose control protocol
		SITA (NIDDM/IDDM)	BITA (NIDDM/IDDM)	SITA	BITA	
Endo 2003 ¹⁵	Yes	NA	NA	92*/†/185‡	80*/†/110‡	NA
Hirotsu 2003 ¹⁶	Yes	NA	NA	NA	NA	NA
Lev-Ran 2003 ¹⁷	Yes	NA	NA	74*	50*	Insulin treatment
Tavolacci 2003 ¹⁸	Yes	NA	NA	NA	NA	NA
Dorman 2004 ¹⁹	Yes	NA	NA	NA	NA	NA
Lev-Ran 2004 ²⁰	Yes	NA	NA	57‡	228‡	Insulin treatment
Stevens 2004 ²¹	Yes	NA	NA	NA	NA	NA
Calafiore 2005 ⁹	Yes	NA	NA	57*/143‡	49*/151‡	Insulin treatment
Momin 2005 ²²	Yes	NA	NA	166*/255‡	95*/218‡	NA
Toumpoulis 2006 ²³	Yes	NA	NA	NA	NA	NA
Savage 2007 ²⁶	NA	83,772/35,289	1320/412	NA	NA	NA
Agrifoglio 2008 ²⁷	NA	34/7	34/6	NA	NA	Insulin treatment
Kinoshita 2010 ⁸	Yes	NA	NA	85*/56†/30‡	81*/59†/31‡	NA
Konstanty-Kalandyck 2012 ²⁴	NA	NA	NA	54*/55‡	23*/15‡	Insulin treatment
Gansera 2016 ²⁹	Yes	75/50	80/45	NA	NA	NA
Puskas 2012 ²⁵	NA	NA	NA	NA	NA	NA
Taggart 2012 ²⁸	NA	284/79	276/95	NA	NA	NA
Pevni 2017 ⁷	NA	411/82	424/63	NA	NA	NA

DM, Diabetes mellitus; SITA, single internal thoracic artery; NIDDM, noninsulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; BITA, bilateral internal thoracic artery; OP, operation; NA, not available. *Insulin control. †Oral agent control. ‡Diet control.

TABLE 4. Description of confounders used in propensity score analysis studies

Study	PSA methodology	Variables
Dorman 2004 ¹⁹	1:1 ratio using a Rosenbaum optimal matching algorithm	Age, cerebrovascular disease, CHF, dyslipidemia, impaired ejection fraction (<0.50), family history of coronary artery disease, hypertension, male gender, PVD, prior MI, renal dysfunction, smoking history, 3-vessel disease, unstable angina
Calafiore 2005 ⁹	1:1 matching method not reported	Age, female, diabetes mellitus on oral treatment, diabetes mellitus on insulin treatment, urgent, extracardiac vasculopathy, preoperative acute MI, unstable angina, CHF, chronic renal failure, COPD, ejection fraction, left main stem, 2-vessel disease, 3-vessel disease, euroSCORE
Toumpoulis 2006 ²³	1:1 ratio using logistic regression analysis	euroSCORE, age, female, race, vessels involved, unstable angina, previous MI (most recent), transmural MI, >1 previous MI, previous cardiac operation, CCS angina class, urgency operation, hemodynamic instability, shock, ejection fraction categories, current CHF, past CHF, PVD, BMI categories, hypertension, COPD, calcified aorta, renal failure, preoperative dialysis, hepatic failure, immune deficiency, preoperative IABP, LV hypertrophy, malignant ventricular arrhythmia, thrombolysis prior surgery, previous PCI, smoking previous year, total bypass time, OPCABG, anastomoses
Kinoshita 2010 ⁸	1:1 ratio using multivariate logistic regression model	Age, female sex, body mass index, main fraction of glycosylated hemoglobin (HgbA1C), PVD, COPD, previous MI, emergency operation, number of target vessels, left main trunk having >50% stenosis, diagonal branch having >75% stenosis, and circumflex artery having >75% stenosis
Ganera 2016 ²⁹	1:1 matching method not reported	Age, gender, number of grafts, elective, urgent/emergency operations, preoperative infarction, PCI, preoperative stent
Pevni 2017 ⁷	1:1 matching method using a saturated logistic regression model	Age, sex, insulin treatment, diabetes with end-organ damage, recent MI, chronic renal failure, congestive heart failure, COPD, unstable angina, number of diseased vessels, neurologic dysfunction, PCI, and ejection fraction ≤30%

PSA, Propensity score analysis; CHF, congestive heart failure; PVD, peripheral vascular disease; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; euroSCORE, European System for Cardiac Operative Risk Evaluation; CCS, Canadian Cardiovascular Society; BMI, body mass index; IABP, intra-aortic balloon pump; LV, left ventricular; OPCABG, off-pump coronary artery bypass grafting; HgbA1C, hemoglobin A1C; PCI, percutaneous coronary intervention.

Quality Assessment

The quality assessment of 17 observational studies are shown in Table 5. According to the Newcastle–Ottawa Scale for this meta-analysis (Table 6), all of these observational studies included scored between 7 and 9, indicating high methodologic quality.

Deep Sternal Wound Infection

In the Forest plots of DSWI shown in Figure 1, A, the overall incidence of DSWI in the BITA grafting group (3.26%) was significantly higher than in the SITA grafting group (1.70%) (RR, 0.64; 95% CI, 0.50-0.81; $P < .001$; $I^2 = 12\%$). The incidence of DSWI in the BITA grafting group (3.27%) was also significantly higher than in the SITA grafting group (1.90%) (RR, 0.60; 95% CI, 0.41-0.87; $P < .001$; $I^2 = 0\%$) in the propensity-matched subgroup⁵ studies in which skeletonized harvesting of the ITA grafts was performed were analyzed. As the Forest plots of DSWI show in Figure 1, B, no significant difference was found between both groups in terms of risk of DSWI when the skeletonized harvesting technique was adopted (2.46% for SITA group vs 2.48% for BITA group, RR, 0.94; 95% CI, 0.55-1.63, $P = .84$, $I^2 = 0\%$). Subpopulation

analysis also demonstrated that no significant difference was found between both groups in terms of risk of DSWI when the skeletonized harvesting technique was adopted (RR, 0.91; 95% CI, 0.49-1.67, $P = .75$, $I^2 = 0\%$).

Early Mortality

Results of in-hospital and 30-day mortality are shown in Figure 2, A. Meta-analysis of the included studies showed that no significant difference was observed in early mortality between the BITA grafting group (2.80%) and the SITA grafting group (2.36%) (RR, 1.16; 95% CI, 0.94-1.42, $P = .17$, $I^2 = 0\%$). Subpopulation analysis also demonstrated that no significant difference was observed in early mortality between both groups (RR, 1.21; 95% CI, 0.87-1.69, $P = .26$, $I^2 = 0\%$).

Long-Term Overall Survival

Results of HR for long-term overall mortality are shown in Figure 2, B. Pooled analysis indicated BITA grafting had a lower risk for long-term overall mortality among diabetic patients when compared with SITA grafting (HR, 1.41; 95% CI, 1.18-1.67, $P < .001$, $I^2 = 63\%$). The BITA cohort also demonstrated a lower risk for

TABLE 5. Quality assessment of included observational studies using Newcastle–Ottawa Assessment Scale

Trials	Selection				Comparability	Outcome			Total score
	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Endo 2003 ¹⁵	*	*	*	*	**	*	*	*	9
Hirotsu 2003 ¹⁶	*	*	*	*	**	*	*	*	9
Lev-Ran 2003 ¹⁷	*	*	*	*	**	*	*	*	9
Tavolacci 2003 ¹⁸	*	*	*	*		*	*	*	7
Dorman 2004 ¹⁹	*	*	*	*	**	*	*		8
Lev-Ran 2004 ²⁰	*	*	*	*	**	*	*	*	9
Stevens 2004 ²¹	*	*	*	*	**	*	*	*	9
Calafiore 2005 ⁹	*	*	*	*	**	*	*	*	9
Momin 2005 ²²	*	*	*	*	**	*	*	*	9
Toumpoulis 2006 ²³	*	*	*	*	**	*	*		8
Savage 2007 ²⁶	*	*	*	*	**	*	*	*	9
Agrifoglio 2008 ²⁷	*	*	*	*	**	*	*	*	9
Kinoshita 2010 ⁸	*	*	*	*	**	*	*	*	9
Konstanty-Kalandyck 2012 ²⁴	*	*	*	*	**	*	*	*	9
Gansera 2016 ²⁹	*	*	*	*	*	*	*	*	8
Puskas 2012 ²⁵	*	*	*	*	**	*	*		8
Pevni 2017 ⁷	*	*	*	*	**	*	*	*	9

*1 point.

long-term overall mortality in the propensity-matched subgroup (HR, 1.34; 95% CI, 1.08-1.67, $P < .001$, $I^2 = 71\%$). Reconstructed individual patient survival data from Kaplan–Meier survival curves of all 10 series demonstrated 1-year, 5-year, 10-year, 15-year, and 20-year overall survivals at 94.33%, 81.31%, 63.30%, 44.42%, and 34.84%, respectively, in the SITA arm and 96.70%, 87.83%, 73.71%, 59.42%, and 46.43%, respectively, in the BITA arm (Figure 3, C). Kaplan–Meier survival curves of all 5 propensity-matched studies demonstrated 1-year, 5-year, 10-year, 15-year, and 20-year overall survivals at 92.98%, 78.20%, 59.10%, 39.65%, and 29.87%, respectively, in the SITA arm and 95.14%, 85.98%, 67.00%, 42.93%, and 31.48%, respectively, in the BITA arm (Figure 3, B).

Long-Term Cardiac Mortality-Free Survival

As the Forest plots of HR for long-term cardiac mortality show in Figure 2, C, HR for long-term cardiac mortality significantly decreased in the BITA cohort compared with the SITA cohort (HR, 3.15; 95% CI, 2.23-4.46, $P < .001$, $I^2 = 0\%$). Reconstructed individual patient survival data from Kaplan–Meier survival curves of all 4 series demonstrated 1-year, 3-year, 5-year, and 8-year cardiac mortality-free survival at 91.27%, 77.40%, 73.61%, and 69.55%, respectively, in the SITA arm and 98.42%, 92.65%, 90.77%, and 89.97%, respectively, in the BITA arm (Figure 4).

Publication Bias Assessment

Neither the Begg rank correlation test ($P = .303$) nor the Egger linear regression method ($P = .417$) suggested publication bias was a significant factor when DSWI was selected as an end point. All 10 studies yield a Begg's test score of $P = .235$ and Egger's test score of $P = .698$ when assessing early mortality. However, evidence of publication bias was identified with long-term overall survival (Begg's $P = .032$; Egger's $P = .014$).

DISCUSSION

This present updated meta-analysis demonstrated that CABG with BITA grafting was not associated with an increased risk of DSWI in diabetic patients when the skeletonized harvesting technique was performed. Furthermore, BITA grafting offered comparable in-hospital mortality and provided long-term overall and cardiac mortality-free survival advantage compared with SITA grafting among diabetic patients.

Over the last decades, the excellent long-term survival of using BITA versus SITA is well established in several existing publications. In light of continuous accumulating evidence in favor of BITA grafting, the recent Clinical Practice Guideline by Society of Thoracic Surgeons recommended that a second skeletonized ITA should be used in patients who do not have an excessive risk of sternal complications (Classification of Recommendation IIa, Level of Evidence B).³⁰ The present meta-analysis also

TABLE 6. Newcastle-Ottawa quality assessment scale for cohort studies

Selection	
1. Representativeness of the exposed cohort	
a. truly representative of the average _____ (describe) in the community*	
b. somewhat representative of the average _____ in the community*	
c. selected group of users, eg, nurses, volunteers	
d. no description of the derivation of the cohort	
2. Selection of the nonexposed cohort	
a. drawn from the same community as the exposed cohort*	
b. drawn from a different source	
c. no description of the derivation of the nonexposed cohort	
3. Ascertainment of exposure	
a. secure record (eg, surgical records)*	
b. structured interview*	
c. written self-report	
d. no description	
4. Demonstration that outcome of interest was not present at start of study	
a. yes*	
b. no	
Comparability	
1. Comparability of cohorts on the basis of the design or analysis	
a. study controls for at least 3 of the following 4 factors: age, sex, coronary anatomy, body mass index (select the most important factor)*	
b. study controls for any additional comorbidities*	
Outcome	
1. Assessment of outcome	
a. independent blind assessment*	
b. record linkage*	
c. self-report	
d. no description	
2. Was follow-up long enough (>1 y, except those studies that only focus on in-hospital mortality and DSWI) for outcomes to occur	
a. yes (select an adequate follow-up period for outcome of interest)*	
b. no	
3. Adequacy of follow-up of cohorts	
a. complete follow-up, all subjects accounted for*	
b. subjects lost to follow-up unlikely to introduce bias, small number lost, ≥95% (select an adequate %) follow-up, or description provided of those lost)*	
c. follow-up rate <95% (select an adequate %) and no description of those lost	
d. no statement	

A study can be awarded a maximum of 1 star for each numbered item within the Selection and Outcome categories. A maximum of 2 stars can be given for Comparability. DSWI, Deep sternal wound infection. *1 point.

demonstrated that BITA grafting significantly increased long-term overall and cardiac mortality-free survival among diabetic patients. However, on average, compared with the SITA cohort, patients allocated to the BITA cohort in this meta-analysis were younger, had less

body mass index, and had lower prevalence of preoperative risks.

Therefore, these confounding factors and selection bias may result in better outcomes of BITA grafting. However, in our meta-analysis, propensity-matched subgroup analysis still presented the same findings, supporting favorable clinical outcomes of BITA grafting in more comparable cohorts.

Diabetes mellitus is a widely recognized risk factor for worse outcomes of patients with multivessel disease undergoing CABG. The histologic and vasophysiologic properties of ITA are relatively protective against endothelial dysfunction, which is one of the important mechanisms underlying diabetes-related cardiovascular disease, and therefore result in favorable graft patency.^{31,32} These mechanisms may explain why BITA could offer better clinical outcomes compared with SITA for diabetic patients.

Although BITA grafting has been found to be associated with a lower risk for long-term mortality than SITA grafting in diabetic patients undergoing CABG, BITA grafting has not been routinely used.³³ Indeed, clinical databases have shown that BITA grafting is used in only 4% of CABG surgeries in the United States³³ and 12% in Europe.³⁴ Compared with SITA grafting, BITA grafting has several drawbacks, including the increased risk of DSWI especially for diabetic patients¹⁰ and longer preparation time and operative time,³⁵ which may be seen as obstacles that could prevent widespread uptake of BITA grafting. In our present meta-analysis, BITA grafting was associated with a higher occurrence of DSWI than SITA grafting for diabetic patients both in the overall unmatched group and propensity-matched subgroup. BITA harvesting could exacerbate an acute postoperative devascularization of the sternum, and therefore increasing the risk of DSWI.³⁶ Although the incidence of DSWI among diabetic patients was relatively low in this present analysis (1.70% for SITA group vs 3.26% for BITA group, $P = .0003$), DSWI has been recognized as a detrimental risk factor for long-term survival.³⁷

However, diabetic patients should not be entirely excluded from BITA grafting because of the increased risk of DSWI. Our data in the present meta-analysis showed that no significant difference was found between SITA grafting and BITA grafting in terms of risk of DSWI when the skeletonized harvesting technique was adopted. In comparison with the pedicled harvesting technique, the skeletonized technique preserves the collateral circulation to the sternum and the drainage of internal thoracic veins and thereby brings a lower risk of sternal infection.³⁸

Preoperative control of glycosylated hemoglobin and postoperative glucose management are also critical to decrease the incidence of DSWI. Elevated preoperative glycosylated hemoglobin in patients presenting for CABG was

FIGURE 1. Forest plots of DSWI. A, Results of all 18 studies. B, Results of 5 studies in which ITA was harvested in a skeletonized fashion. Results are shown as RR with 95% CI. *SITA*, Single internal thoracic artery; *BITA*, bilateral internal thoracic artery; *M-H*, Mantel-Haenszel; *CI*, confidence interval; *df*, degrees of freedom; *SE*, standard error; .

FIGURE 2. Forest plots of mortality and survival. A, Results for early death. B, Results for HR of long-term overall mortality. C, Results for HR of long-term cardiac mortality. Results are shown as RR or HR with 95% CI. *SITA*, Single internal thoracic artery; *BITA*, bilateral internal thoracic artery; *M-H*, Mantel-Haenszel; *CI*, confidence interval; *df*, degrees of freedom; *SE*, standard error.

FIGURE 3. Overall Kaplan-Meier survival curves based on reconstructed individual patient data. A, Aggregated survival curve for long-term overall survival with data of 1990 patients in SITA cohort and 914 patients in BITA cohort from 5 unmatched studies. B, Aggregated survival curve for long-term overall survival with data of 1764 patients in SITA cohort and 1764 patients in BITA cohort from 5 matched studies. C, Aggregated survival curve for long-term overall survival with data of 3754 patients in SITA cohort and 2678 patients in BITA cohort from 10 studies. *SITA*, Single internal thoracic artery; *BITA*, bilateral internal thoracic artery.

FIGURE 4. Aggregated survival curve for cardiac mortality-free survival with data of 501 patients in SITA cohort and 648 patients in BITA cohort from 4 studies. *SITA*, Single internal thoracic artery; *BITA*, bilateral internal thoracic artery.

associated with a significant increase in the incidence of DSWI.^{39,40} In the present meta-analysis, 2 studies^{8,27} recorded the data of HgbA1c before operation (Kinoshita and colleagues⁸: $6.1\% \pm 2.1\%$ for SITA vs $6.3\% \pm 2.4\%$ for BITA; Agrifoglio and colleagues²⁷: $8.3\% \pm 0.9\%$ for SITA vs $8.6\% \pm 1.0\%$ for BITA). In addition, intensive glucose control was associated with a reduction of DSWI and mortality after CABG, as previously reported by Furnary and associates.⁴¹ In our meta-analysis, 5 studies^{9,17,20,24,27} described a specific protocol for postoperative glucose control, which was intensive glucose control by continuous insulin infusion, and similar incidences of DSWI between SITA and BITA cohort were reported.

Study Limitations

The results of the present meta-analysis were limited by several restraints and should be interpreted with caution. First, most of the included studies were retrospective analyses in nature, and some studies were not propensity score matched; therefore, intrinsic patient selection bias and significant confounding factors may affect the difference in observed outcomes. Second, variations in expertise and the rate of off-pump CABG of different centers could also account for clinical heterogeneity. Third, compared with SITA grafting, BITA grafting was typically preferred for

term overall survival with data of 1764 patients in SITA cohort and 1764 patients in BITA cohort from 5 matched studies. C, Aggregated survival curve for long-term overall survival with data of 3754 patients in SITA cohort and 2678 patients in BITA cohort from 10 studies. *SITA*, Single internal thoracic artery; *BITA*, bilateral internal thoracic artery.

VIDEO 1. Pengyu Zhou, MD, presents the results of this study. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)30452-0/fulltext](https://www.jtcvs.org/article/S0022-5223(19)30452-0/fulltext).

those with less preoperative risk profile, and therefore, it may naturally result in more favorable long-term survival in the BITA grafting group.

CONCLUSIONS

Compared with SITA grafting, BITA grafting increases the risk of DSWI in diabetic patients, although this is an infrequent risk. However, skeletonization of BITA is not associated with an increased risk of DSWI. Furthermore, BITA grafting is associated with superior overall late survival and increased cardiac mortality-free survival. In light of these findings, the long-term advantage of BITA outweighs its short-term risk. Therefore, surgeons should be encouraged to adopt BITA grafting in a skeletonized manner more routinely in diabetic patients.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: bilateral internal thoracic artery grafting, coronary artery bypass grafting, diabetes, skeletonization

FIGURE E1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart for literature search. *DM*, Diabetes mellitus; *ITA*, internal thoracic artery.

TABLE E1. Main characteristics of patients in included studies

Patient baseline	No. of studies reporting variables	Report No. of patients		OR/mean difference, 95% CI	P value
		SITA	BITA		
Mean age, y	14	121,940	4355	2.54 [0.98-4.10]	.001*
Female gender, N	15	122,167	4545	1.42 [1.14-1.77]	.002*
BMI, mean (SD)	7	119,991	2654	0.59 [0.16-1.02]	.007*
Preoperative characteristics					
COPD, N	9	121,043	3330	1.42 [1.22-1.65]	.001*
HTN, N	8	2241	1812	1.13 [0.81-1.58]	.48
Renal impairment, N	8	120,868	3360	1.66 [1.18-2.33]	.004*
Prior CVD, N	7	1709	1656	1.46 [0.66-3.24]	.35
Prior MI, N	12	121,689	4226	1.08 [0.94-1.24]	.30
Intraoperative characteristics					
No. of grafts, mean (SD)	10	2057	1854	−0.22 [−0.35 to −0.08]	.002*
CPB, min	5	1076	1222	−8.43 [−22.37 to 5.50]	.24
Crossclamping time, min	6	819	949	−5.97 [−11.23 to −0.71]	.03*

OR, Odds ratio; CI, confidence interval; SITA, single internal thoracic artery; BITA, bilateral internal thoracic artery; N, number of patients; BMI, body mass index; SD, standard deviation; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HTN, hypertension; CVD, cerebrovascular disease; MI, myocardial infarction; CPB, cardiopulmonary bypass; CVD, cerebrovascular disease; HTN, hypertension; MI, myocardial infarction; N, number of patients, OR, odds ratio; PVD, peripheral vascular disease; SD, standard deviation; SITA, single internal thoracic artery. *Statistically significant.