Surgical revascularization techniques that minimize surgical risk and maximize late survival after coronary artery bypass grafting in patients with diabetes mellitus

Sajjad Raza, MD,^a Joseph F. Sabik III, MD,^a Khalil Masabni, MD,^a Ponnuthurai Ainkaran, MS,^b Bruce W. Lytle, MD,^a and Eugene H. Blackstone, MD^{a,b}

Objective: To identify surgical revascularization techniques that minimize surgical risk and maximize late survival in patients with diabetes undergoing coronary artery bypass grafting (CABG).

Methods: From January 1972 to January 2011, 11,922 patients with diabetes underwent primary isolated CABG. The revascularization techniques investigated included bilateral internal thoracic artery (BITA) grafting (n = 938; 7.9%) versus single ITA (SITA) grafting, off-pump (n = 602; 5.0%) versus on-pump CABG, and incomplete (n = 2109; 18%) versus complete revascularization. The median follow-up was 7.8 years and total follow-up, 104,516 patient-years. Multivariable analyses were performed to assess the effects of surgical techniques on hospital outcomes and long-term mortality.

Results: After adjusting for patient characteristics, BITA versus SITA grafting was associated with a 21% lower late mortality (68% confidence limits, 16%-26%). However, BITA grafting was also associated with more deep sternal wound infections (DSWIs), but the considerable mortality from DSWI minimally affected overall survival because of its rare occurrence. The risk factors for DSWI were female sex (80% increased risk), higher body mass index (7% increased risk per kg/m²), medically treated diabetes (73% increased risk), previous myocardial infarction (58% increased risk), and peripheral arterial disease (73% increased risk). Off-pump and on-pump CABG had similar results. Complete versus incomplete revascularization had similar hospital outcomes; however, complete revascularization was associated with 10% lower late mortality (68% confidence limits, 7.0%-13%).

Conclusions: BITA grafting with complete revascularization maximizes long-term survival and is recommended for patients with diabetes undergoing CABG. BITA grafting should be used in all patients with diabetes whose risk of DSWI is low. It might be best avoided in obese diabetic women with diffuse atherosclerotic burden—those at greatest risk of developing these infections. (J Thorac Cardiovasc Surg 2014;148:1257-66)

Supplemental material is available online.

From the Department of Thoracic and Cardiovascular Surgery,^a Heart and Vascular Institute, and Department of Quantitative Health Sciences,^b Research Institute, Cleveland Clinic, Cleveland, Ohio.

The present study was supported in part by the Sheikh Hamdan bin Rashid Al Maktoum Distinguished Chair in Thoracic and Cardiovascular Surgery, held by Dr Sabik, and the Kenneth Gee and Paula Shaw, PhD, Chair in Heart Research, held by Dr Blackstone.

Disclosures: Dr Sabik is the North American principal investigator for the Abbott Laboratories-sponsored left main coronary disease randomized trial (EXCEL) and is on the Society for Thoracic Surgeons board of directors and the scientific advisory board of Medtronic. All other authors have nothing to disclose with regard to commercial support.

Read at the 94th Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada, April 26-30, 2014.

Received for publication April 16, 2014; revisions received June 17, 2014; accepted for publication June 27, 2014.

Address for reprints: Joseph F. Sabik III, MD, Department of Thoracic and Cardiovascular Surgery, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Ave, Desk J4-1, Cleveland, OH 44195 (E-mail: sabikj@ccf.org).

0022-5223/\$36.00

Copyright © 2014 Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2014.06.058>

The FREEDOM trial (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal Management of multivessel disease) showed that coronary artery bypass grafting (CABG) should be the preferred revascularization strategy for patients with diabetes mellitus with multivessel coronary artery disease (CAD).¹ However, it did not attempt to answer the important question of which surgical revascularization techniques will optimize the outcomes of CABG in these patients. Therefore, to identify the techniques that minimize surgical risk and maximize late survival, we studied the comparative effectiveness of (1) single internal thoracic artery (SITA) versus bilateral internal thoracic artery (BITA) grafting, (2) complete versus incomplete revascularization, and (3) off-pump versus on-pump CABG for diabetic patients undergoing CABG.

METHODS

From January 1972 to January 2011, 11,922 diabetic patients underwent primary isolated CABG at Cleveland Clinic (Table E1). The type of diabetes management was known for 8196 patients—2743 insulin-treated, 3766 non-insulin-treated, and 1687 diet-controlled. The surgical revascularization techniques investigated included (1) SITA (n = 8466; 71%) and BITA (n = 938; 7.9%) grafting with or without other grafts

Abbreviations and Acronyms

BITA	= bilateral internal thoracic artery
BMI	= body mass index
CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
DSWI	= deep sternal wound infection
ITA	= internal thoracic artery
SITA	= single internal thoracic artery
STS	= Society of Thoracic Surgeons
SVG	= saphenous vein grafting

versus saphenous vein grafting (SVG) alone ($n = 2491$; 21%). SITA versus BITA grafting was investigated in patients with multivessel CAD ($n = 11,322$, 95% of the total study cohort), (2) incomplete ($n = 2109$; 18%) versus complete revascularization, and (3) off-pump ($n = 602$; 5.0%) versus on-pump CABG. The patients were identified and the preoperative, operative, and postoperative variables retrieved from the prospective computerized Cardiovascular Information Registry of the Heart and Vascular Institute. The institutional review board approved this database for use in research, with patient consent waived.

Variables and Definitions

A coronary artery system was considered importantly stenotic if it contained a $\geq 50\%$ -diameter obstruction. Incomplete revascularization was defined as failure to graft any system containing $\geq 50\%$ stenosis or both the left anterior descending and circumflex coronary artery systems for $\geq 50\%$ left main trunk stenosis.

Endpoints

The endpoints of the present study were (1) in-hospital outcomes with morbidities defined as for the Society of Thoracic Surgeons (STS) national database (available at: http://www.sts.org/sites/default/files/documents/word/STSAAdultCVDataSpecificationsV2_73%20with%20correction.pdf), and (2) long-term all-cause mortality. Patients' vital status after hospital discharge was obtained from the Cardiovascular Information Registry routine anniversary follow-up information supplemented with data from the Social Security Death Master File^{2,3} (accessed October 29, 2011); the closing date was set 6 months earlier (April 27, 2011). The median follow-up was 7.8 years, with 104,516 patient-years of data available for analysis. Twenty-five percent of the survivors had been followed up for >13 years and 10% for >19 years.

Statistical Analysis

In-hospital outcomes. Multivariable logistic regression (PROC LOGISTIC, SAS Institute, Inc, Cary, NC) was used to identify the factors associated with each postoperative in-hospital complication (ie, hospital death, deep sternal wound infection [DSWI], stroke, reoperation for bleeding, length of stay >14 days, renal failure, and prolonged ventilation [>24 hours]). Using only preoperative patient variables (Appendix E1), we first formed a risk factor (patient) model. For this, variable screening, with a P value criterion for retention of variables in the model of .05, used a computer-intensive machine-learning "bagging" method (bootstrap aggregation).^{4,5} Variables with bootstrap reliability of $\geq 50\%$ were included in the model. We then augmented the patient model with the surgical techniques and variables related to diabetes treatment, irrespective of their statistical significance. We also performed subgroup analyses for the patients with multivessel disease ($n = 11,322$,

95% of the total study cohort) to assess the effect of BITA versus SITA grafting.

Survival. Nonparametric survival estimates were obtained using the Kaplan-Meier method and parametric estimates using a multiphase nonproportional hazards model.⁶ The parametric method was used to resolve the number of phases of instantaneous risk of death (hazard function). Multivariable analysis was performed in the hazard function domain, incorporating the risk factors simultaneously into all phases. Variable screening, formation of a patient and augmented model, and subgroup analyses for patients with multivessel disease were performed as described.

Missing values. A number of variables examined in the multivariable analyses had missing values. We used fivefold multiple imputation⁷ by a Markov chain Monte Carlo technique (SAS PROC MI and SAS PROC MIANALYZE; SAS Institute, Inc).

Patients deriving maximum benefit from optimal

strategy. To identify the patients deriving the greatest survival benefit from an optimal surgical technique, the multivariable hazard model was solved for each patient in the study to produce the 10-year predicted survival using 12 possible surgical combinations (derived from no ITA, 1 ITA, 2 ITAs, incomplete revascularization, complete revascularization, off-pump CABG, and on-pump CABG). Next, using cumulative distributions of 10-year predicted survival for each of the 12 possible surgical combinations, we identified the combinations with the best and worst 10-year predicted survival. The difference between the best and worst 10-year predicted survival was calculated for each patient. A logistic model was then fitted for the highest quintile group.

DSWI and mortality. The survival of patients after diagnosis of a postoperative DSWI was assessed nonparametrically using the Kaplan-Meier method. The effect of DSWI on time-related mortality for the BITA and SITA groups as a whole was assessed by comparing nonparametric survival with and without DSWI.

Presentation. Continuous variables are summarized as the mean $\pm$ standard deviation; comparisons were made using the Wilcoxon rank-sum (nonparametric) test. Categorical data are summarized as frequencies and percentages; comparisons were made using the chi-square test or Fisher's exact test, when the frequency was <5 . Transformation of scale of the continuous variables was necessary to meet the statistical model assumptions; therefore, the results of the logistic and multiphase hazard models are presented with their coefficients rather than odds or hazard ratios. All analyses were performed using SAS, version 9.1, statistical software (SAS Institute, Inc). Uncertainty is expressed by confidence limits (CL) equivalent to ± 1 standard error (68%). Graphics were constructed using either SAS software (SAS Institute, Inc) or the R package (R Project for Statistical Computing, Vienna, Austria).

RESULTS**Hospital Outcomes**

Effect of BITA versus SITA. For patients undergoing BITA or SITA grafting, hospital mortality (0.75% vs 1.2%, $P = .11$) and the prevalence of stroke (0.96% vs 1.7%, $P = .10$) were similar. However, BITA grafting was associated with a higher occurrence of DSWI (3.4% vs 2.1%, $P = .01$) and reoperation for bleeding (4.4% vs 3%, $P = .04$). SITA grafting was associated with a higher occurrence of renal failure (4.1% vs 1.9%, $P = .002$), prolonged ventilation (11% vs 4%, $P = .001$), and postoperative length of stay >14 days (8.2% vs 6.0%, $P = .004$; Figure 1, Table E2). After multivariable risk

FIGURE 1. Comparative risk of developing complications after coronary artery bypass grafting in diabetic patients. An odds ratio of 1.0 indicates equal risk; odds ratios >1.0 indicate greater risk and those <1.0, lower risk. Symbols represent point estimates and horizontal bars, 68% confidence limits equivalent to ± 1 standard error. A and B, Bilateral (BITA) versus single (SITA) internal thoracic artery grafting. C and D, Incomplete versus complete revascularization. E and F, Off- versus on-pump surgery. *Reop*, Reoperation; *Postop*, postoperative; *LOS*, length of stay; *SWI*, sternal wound infection.

adjustment, BITA was associated with a higher risk of DSWI ($P = .0002$) and reoperation for bleeding ($P = .03$), but with a lower risk of prolonged ventilation ($P = .04$; Figure 1, Table 1, Tables E3-E8).

Effect of complete versus incomplete revascularization. In patients undergoing complete versus incomplete revascularization, hospital mortality (1.8% vs 2.2%, $P = .2$), DSWI (2.2% vs 2.0%, $P = .6$), stroke (2.0% vs 2.5%, $P = .2$), renal failure (3.8% vs 3.4%, $P = .4$), reoperation for bleeding (3.4% vs 3.1%, $P = .4$), postoperative length of stay >14 days (9.1% vs 9.2%, $P > .9$), and prolonged ventilation (11% vs 13%, $P = .5$) were similar (Figure 1, Table E2). After adjustment, all hospital outcomes were similar, with the possible exception

of a higher risk of reoperation for bleeding ($P = .06$) with complete revascularization (Figure 1, Table 1, Tables E3-E8).

Effect of off-pump versus on-pump CABG. In patients undergoing off- or on-pump surgery, hospital mortality (1.2% vs 1.9%, $P = .18$), DSWI (1.3% vs 2.2%, $P = .15$), stroke (1.3% vs 2.2%, $P = .17$), reoperation for bleeding (2.7% vs 3.4%, $P = .3$), postoperative length of stay >14 days (8.1% vs 9.2%, $P = .4$), and prolonged ventilation (11% vs 11%, $P > .9$) were similar. However, the occurrence of renal failure was greater with off-pump surgery (7.6% vs 3.5%, $P < .0001$; Figure 1, Table E2). After adjustment, all in-hospital outcomes were similar (Figure 1, Table 1, Tables E3-E8).

TABLE 1. Risk factors for deep sternal wound infection

Factor	Estimate $\pm$ SE	OR (68% CL)	P value	Reliability (%) [*]
Demographic data				
Female sex	0.59 $\pm$ 0.59	1.80 (1.64-1.99)	<.0001	88
BMI	0.057 $\pm$ 0.01 [†]	—	<.0001	84
Cardiac comorbidity				
Previous MI	0.46 $\pm$ 0.13	1.58 (1.39-1.80)	.0006	89
Noncardiac comorbidity				
PAD	0.55 $\pm$ 0.15	1.73 (1.49-2.01)	.0003	83
Diabetes				83
Pharmacologically treated	0.55 $\pm$ 0.24	1.73 (1.36-2.20)	.02	
Insulin treated	−0.0094 $\pm$ 0.16	0.99 (0.84-1.16)	>.9	
Procedure				
ITA graft				95
Single (vs SVG only)	0.27 $\pm$ 0.19	1.31 (1.08-1.58)	.15	
Bilateral (vs SVG only)	1.01 $\pm$ 0.25	2.75 (2.14-3.53)	<.0001	
Bilateral vs single [‡]	0.74 $\pm$ 0.20	2.09 (1.72-2.56)	.0003	
Incomplete revascularization (vs complete)	−0.14 $\pm$ 0.18	0.87 (0.73-1.04)	.4	2 [§]
Off-pump surgery (vs on-pump)	−0.44 $\pm$ 0.37	0.64 (0.54-0.77)	.2	28 [§]
Earlier date of operation	−0.026 $\pm$ 0.0085 [‡]	—	.0025	35 [§]

C-statistic = 0.67. SE, Standard error; OR, odds ratio; CL, confidence limits; BMI, body mass index; MI, myocardial infarction; PAD, peripheral arterial disease; ITA, internal thoracic artery; SVG, saphenous vein graft. ^{*}Percentage of times the factor appeared in 500 bootstrap models. [†]See Figure E1. [‡]Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. [§]Variables were forced into model, even though the reliability was low. ^{||}Date of operation (years since January 1, 1972).

Effect of diabetes management. After risk adjustment, pharmacologically treated diabetes was associated with a higher risk of DSWI, stroke, and prolonged length of stay (Table 1, Tables E3-E8). No statistically significant effect was found for pharmacologically treated diabetes on in-hospital death, renal failure, or reoperation for bleeding, nor was an effect found for insulin versus non-insulin-treated diabetes on in-hospital outcomes.

Patient factors associated with increased risk of DSWI.

The risk factors for DSWI included female sex (80% increased risk), higher body mass index (BMI) (7% increased risk per kg/m²; Figure E1, A), medically treated diabetes (73% increased risk compared with diet-controlled diabetes), previous myocardial infarction (58% increased risk), peripheral arterial disease (73% increased risk), and BITA versus SITA grafting (118% increased risk; Table 1). The risk of DSWI decreased steadily during the study period (Figure E1, B). For example, a diabetic man with a BMI of 40 kg/m² had a lower risk of developing DSWI than a diabetic woman with a BMI of 30 kg/m² (Figure 2, A). A female patient with a BMI > 30 kg/m², peripheral arterial disease, previous myocardial infarction, and pharmacologically treated diabetes had the greatest risk of developing a DSWI after BITA grafting (Figure 2, B). A medically treated diabetic patient undergoing BITA grafting had a greater risk of developing DSWI than a diet-controlled diabetic patient undergoing BITA grafting. The hemoglobin A1c level was not associated with DSWI occurrence (Table E9).

Early and Late Survival

Unadjusted. Survival at 30 days and 5, 10, and 20 years was 96%, 75%, 47%, and 15% after SVG alone, 98%, 82%, 58%, and 21% after SITA grafting with or without other grafts, and 99%, 91%, 76%, and 37% after BITA grafting with or without other grafts, respectively ($P[\log\text{-rank}] < .0001$; Figure 3, A). At these same points, corresponding survival after incomplete revascularization was 97%, 78%, 52%, and 18% versus 98%, 82%, 57%, and 21% for complete revascularization ($P[\log\text{-rank}] = .0006$; Figure 3, B) and 98%, 76%, and 56% (no 20-year estimate) after off-pump CABG versus 98%, 81%, 56%, and 20% (with 20-year estimate) after on-pump CABG ($P[\log\text{-rank}] = .4$; Figure 3, C).

Adjusted. After adjustment for patient characteristics, SITA grafting with or without other grafts versus SVG alone was associated with 50% lower (68% CL, 44%-55%) early mortality and 16% lower (68% CL, 14%-19%) late mortality. BITA grafting with or without other grafts was associated with 68% lower (68% CL, 54%-77%) early mortality and 33% lower (68% CL, 28%-37%) late mortality (Figure 4, Table 2). BITA versus SITA grafting was associated with 21% (68% CL, 16%-26%) lower late mortality in patients with multisystem disease (Table E10). Incomplete revascularization was associated with 10% higher (68% CL, 6%-13%) late mortality. Off-pump CABG was associated with 10% lower late mortality than on-pump CABG, but the difference was not statistically significant ($P = .2$).

FIGURE 2. Effect of risk factors on probability of deep sternal wound infection (DSWI) across a range of body mass indexes. Simulations were based on the logistic regression model (Table 1) for a patient undergoing coronary artery bypass grafting with cardiopulmonary bypass, in the past decade, with complete revascularization. Other factors are listed for the individual depictions. A, Effect of female sex after bilateral (BITA) and single (SITA) internal thoracic artery grafting. Simulations are based on an insulin-treated patient with no history of peripheral arterial disease (PAD) or myocardial infarction (MI). B, Effect of PAD and MI after BITA grafting. Simulations are based on an insulin-treated woman. C, Effect of diet-controlled versus medically treated diabetes. Simulations are based on a man with no history of PAD or MI undergoing CABG with BITA grafting.

Effect of diabetes management on survival. Risk-adjusted analyses showed that pharmacologically (insulin or non-insulin) treated diabetes compared with diet-controlled diabetes was associated with a higher risk

FIGURE 3. Unadjusted survival after coronary artery bypass grafting. Each symbol represents a death at selected points (1, 3, 5, 10, 15, and 20 years after surgery) from Kaplan-Meier estimation; vertical bars are confidence limits equivalent to ± 1 standard error (SE). Solid lines are parametric estimates enclosed within dashed confidence bands equivalent to ± 1 SE. A, Stratified by bilateral and single internal thoracic artery grafting and saphenous vein grafting only. B, Stratified by incomplete versus complete revascularization. C, Stratified by off- versus on-pump coronary artery bypass grafting. BITA, Bilateral internal thoracic artery; SITA, single internal thoracic artery; SVG, saphenous vein grafting.

of late death (Table 2). The early and late risk of death was similar for insulin- and non-insulin-treated diabetes.

Effect of occurrence of DSWI on survival. DSWI was associated with a high risk of death within the first year, irrespective of the type of grafting used (Figure E2, A).

FIGURE 4. Risk-adjusted effect of bilateral (*BITA*) versus single (*SITA*) internal thoracic artery grafting and incomplete (*IR*) versus complete (*CR*) revascularization on predicted survival after coronary artery bypass grafting (*CABG*) in diabetic patients. Simulations were based on the multivariable model (Table 2), with the following variables held constant: 62-year-old non-insulin-treated diabetic man, New York Heart Association functional class II, preoperative cholesterol 200 mg/dL, bilirubin 0.6 mg/dL, creatinine 0.8 mg/dL, no carotid disease, heart failure, previous myocardial infarction, peripheral arterial disease, previous stroke, and on-pump coronary artery bypass grafting. *SVG*, Saphenous vein grafting.

However, because of its rare occurrence, it had little effect on overall survival (Figure E2, B).

Patients benefiting most from best versus worst combination of surgical techniques. We identified BITA plus complete revascularization plus off-pump CABG as the strategy with the best predicted survival, and no ITA grafts plus incomplete revascularization plus on-pump CABG with the worst (Figure E3, A). The survival benefit associated with the best combination of surgical techniques was driven by BITA grafting (Figure E3, B), with little increment of benefit from either complete revascularization (Figure E3, C) or off-pump CABG (Figure E3, D). We found that patients deriving the greatest survival benefit (greater than a 23% 10-year survival difference) from the best surgical combination were actually the sickest of all (Table 3, Figure E4)—older women undergoing emergency surgery, with higher bilirubin, previous stroke, peripheral arterial disease, and insulin-treated diabetes.

DISCUSSION

Principal Findings

Our study has shown that for patients with diabetes undergoing CABG, BITA grafting with complete revascularization results in the best long-term survival, whereas off-pump versus on-pump surgery resulted in similar long-term survival. Although BITA grafting was associated with a higher risk of DSWI than SITA grafting or SVG, the considerable mortality from DSWI minimally affected overall survival because of its rare occurrence. We also found

TABLE 2. Incremental risk factors for death after coronary artery bypass grafting

Risk factor	Coefficient $\pm$ SE	P value	Reliability (%) [*]
Early hazard phase			
Demographic data			
Female sex	0.38 $\pm$ 0.10	.0002	99
Older age [†]	0.49 $\pm$ 0.074	<.0001	100
Acuity			
NYHA functional class			93
II	−0.44 $\pm$ 0.15	.003	
III-IV	−0.10 $\pm$ 0.14	.5	
Emergency surgery	1.39 $\pm$ 0.15	<.0001	100
Noncardiac comorbidity			
Diabetes			74
Treated	0.29 $\pm$ 0.18	.10	
Insulin treated	0.20 $\pm$ 0.12	.08	
PAD	0.50 $\pm$ 0.11	<.0001	84
Previous stroke	0.58 $\pm$ 0.13	<.0001	87
Lower cholesterol [‡]	0.10 $\pm$ 0.022	<.0001	59
Higher bilirubin	0.16 $\pm$ 0.051	.002	74
Procedure			
ITA graft			99
Single	−0.69 $\pm$ 0.11	<.0001	
Bilateral	−1.13 $\pm$ 0.35	.001	
Incomplete	0.19 $\pm$ 0.12	.11	10§
revascularization			
Off-pump surgery	−0.03 $\pm$ 0.11	.8	<1§
More recent date of operation	0.00094 $\pm$ 0.0039	.8	24§
Late hazard phase			
Demographic data			
Female sex	0.085 $\pm$ 0.032	.010	75
Older age¶	1.02 $\pm$ 0.064	<.0001	100
Cardiac comorbidity			
Heart failure	0.48 $\pm$ 0.040	<.0001	100
Noncardiac comorbidity			
Diabetes			100
Treated	0.43 $\pm$ 0.044	<.0001	
Insulin treated	0.052 $\pm$ 0.039	.18	
PAD	0.42 $\pm$ 0.033	<.0001	100
Previous MI	0.12 $\pm$ 0.026	<.0001	99
Previous stroke	0.27 $\pm$ 0.049	<.0001	100
Carotid disease	0.13 $\pm$ 0.039	.0006	90
Higher creatinine#	0.14 $\pm$ 0.099	.2	100
Procedure			
ITA graft			100
Single	−0.18 $\pm$ 0.031	<.0001	
Bilateral	−0.40 $\pm$ 0.067	<.0001	
Incomplete	0.091 $\pm$ 0.032	.004	36§
revascularization			
Off-pump surgery	−0.096 $\pm$ 0.081	.2	<1§

SE, Standard error; NYHA, New York Heart Association; PAD, peripheral arterial disease; ITA, internal thoracic artery; MI, myocardial infarction. ^{*}Percentage of times the factor appeared in 500 bootstrap models. [†]Exp(age/50), exponential transformation. [‡](1/Cholesterol)², inverse squared transformation. [§]Variables were forced into the model, even though the reliability was low. ^{||}Date of operation (years since January 1, 1972). [¶](50/Age)², inverse squared transformation. [#]Log(creatinine), logarithmic transformation.

TABLE 3. Risk factors associated with maximum survival benefit from optimal combination of surgical techniques (BITA + complete revascularization + off-pump)

Factor	Estimate ± SE	OR (68% CL)	P value
Demographic data			
Female sex	1.86 ± 0.097	6.4 (5.8-7.1)	<.0001
Older age*	2.6 ± 0.086†	—	<.0001
Acuity			
NYHA functional class			<.0001
II	−2.1 ± 0.13	0.12 (0.11-0.14)	
III-IV	−0.43 ± 0.11	0.65 (0.58-0.73)	
Emergency surgery	6.0 ± 0.23	410 (330-520)	<.0001
Cardiac comorbidity			
Heart failure	−1.68 ± 0.13	0.19 (0.16-0.21)	<.0001
Noncardiac comorbidity			
Diabetes			<.0001
Pharmacologically treated	1.30 ± 0.20	3.7 (3.0-4.5)	
Insulin treated	0.90 ± 0.095	2.5 (2.2-2.7)	
PAD	2.5 ± 0.10	11.8 (10.7-13.1)	<.0001
Previous stroke	2.4 ± 0.12	10.8 (9.6-12.2)	<.0001
Lower cholesterol‡	1.19 ± 0.15†	—	<.0001
Higher bilirubin	0.58 ± 0.11†	—	<.0001

Reliability, defined as the number of times the factor appeared in 500 bootstrap models, was 100% for all factors; C-statistic = 0.96. *SE*, Standard error; *OR*, odds ratio; *CL*, confidence limits; *NYHA*, New York Heart Association; *PAD*, peripheral arterial disease. *Exp(age/50), exponential transformation. †See Figure E4. ‡(1/Preoperative cholesterol), inverse transformation.

that obese diabetic women with diffuse atherosclerotic burden were at the greatest risk of developing DSWIs.

BITA Versus SITA Grafting

BITA grafting has been found to be associated with better long-term survival than SITA grafting in both diabetic and nondiabetic patients undergoing CABG.⁸⁻¹⁴ Nevertheless, BITA grafting was performed in only 4.4% of CABG cases in the STS national database in 2011.^{15,16} This might have been due to the fear of an increased risk of DWSI,¹⁶ a tradeoff with the long-term survival benefit. This increased risk is of particular concern for those with diabetes, because they are already at a greater risk than those without diabetes of developing surgical site infections. Our data show that BITA grafting is associated with a higher occurrence of DSWI than SITA grafting. However, although we found that DSWI after BITA or SITA grafting was associated with a high risk of death within the first year, it minimally affected overall survival because of its rare occurrence. We identified female sex, higher BMI, previous myocardial infarction, peripheral arterial disease, and medically treated versus diet-controlled diabetes as risk factors associated with the greatest risk of developing DSWI. In addition, we found that some of the factors associated with the greatest risk of developing DSWI after BITA grafting were also associated with deriving the greatest survival

benefit from it. A recent study has also shown that obese diabetic women are at high risk of developing DSWI with BITA grafting.¹⁷ Moreover, we recommend using a skeletonized approach instead of a pedicled approach for harvesting ITAs because the former has been shown to be associated with a lower risk of DSWI in patients with diabetes.¹⁸ At our center, ITA harvesting is done using the skeletonized approach.

Complete Versus Incomplete Revascularization

Early studies of CABG highlighted the survival advantage of complete over incomplete revascularization.¹⁹⁻²¹ Since then, a number of studies have evaluated this effect; however, the literature specifically focusing on patients with diabetes is sparse. Also, the definitions of complete and incomplete revascularization have remained controversial, with different studies reporting different definitions.²² We found that incomplete revascularization was associated with a higher risk of late death, highlighting the importance of the completeness of revascularization for long-term survival benefit. A post hoc analysis from the BARI 2D (Bypass Angioplasty Revascularization Investigation) trial also showed that less complete revascularization was associated with a higher risk of long-term cardiovascular events in those with diabetes.²³

Off-Pump Versus On-Pump CABG

Although a number of studies have compared the outcomes of off-pump versus on-pump CABG,²⁴⁻³¹ few have done so for diabetic populations.³²⁻³⁵ The available studies have shown that in diabetic patients, off-pump CABG results in lower in-hospital morbidity and mortality and higher 1-year survival.³²⁻³⁴ However, our study shows that the hospital outcomes and long-term survival of patients undergoing off-pump or on-pump surgery are similar. Therefore, both strategies represent skill sets that surgeons can use selectively. This is particularly relevant for patients with a greater risk of developing complications from cardiopulmonary bypass or aortic manipulation, because they will benefit the most from off-pump surgery.

Study Limitations

This was a nonrandomized, observational, comparative effectiveness study; thus, patient characteristics might have influenced our findings. To account for this, we performed multivariable adjustment. However, any patient factors importantly affecting outcomes that were not included in the analyses could have biased our findings. Because 4 decades of data from diabetic patients undergoing CABG were used for the analyses, the applicability of our results to contemporary patients could be questionable. To account for this, we adjusted for the date of surgery in each outcome model. BITA grafting, incomplete revascularization, and off-pump CABG all

represent small subsets of our study, which might have limited our ability to identify small incremental benefits within the 12 combinations of surgical strategies analyzed.

CONCLUSIONS

BITA grafting with complete revascularization maximizes long-term survival in patients with diabetes undergoing surgical revascularization. Therefore, BITA grafting should be used for all diabetic patients for whom the risk of DSWI is low. It might be best to avoid BITA grafting in obese diabetic women with diffuse atherosclerotic burden—patients at the greatest risk of developing these infections. Off-pump or on-pump surgery can be used with equal effectiveness, and every effort should be made to completely revascularize the patient.

References

- Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, et al. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012;367:2375-84.
- Boyle CA, Decoufle P. National sources of vital status information: extent of coverage and possible selectivity in reporting. *Am J Epidemiol*. 1990;131:160-8.
- Newman TB, Brown AN. Use of commercial record linkage software and vital statistics to identify patient deaths. *J Am Med Inform Assoc*. 1997;4:233-7.
- Breiman L. Bagging predictors. *Machine Learning*. 1996;24:123-40.
- Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. *Stat Med*. 1992;11:2093-109.
- Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. *J Am Stat Assoc*. 1986;81:615-24.
- Rubin DB. *Multiple Imputation for Non-Response in Surveys*. New York: Wiley; 1987.
- Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. *Ann Thorac Surg*. 2010;90:101-8.
- Lytle BW, Blackstone EH, Loop FD, Houghtaling PL, Arnold JH, Akhrass R, et al. Two internal thoracic artery grafts are better than one. *J Thorac Cardiovasc Surg*. 1999;117:855-72.
- Lytle BW, Blackstone EH, Sabik JF, Houghtaling P, Loop FD, Cosgrove DM. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. *Ann Thorac Surg*. 2004;78:2005-14; discussion 14.
- Endo M, Nishida H, Tomizawa Y, Kasanuki H. Benefit of bilateral over single internal mammary artery grafts for multiple coronary artery bypass grafting. *Circulation*. 2001;104:2164-70.
- Dorman MJ, Kurlansky PA, Traad EA, Galbut DL, Zucker M, Ebra G. Bilateral internal mammary artery grafting enhances survival in diabetic patients: a 30-year follow-up of propensity score-matched cohorts. *Circulation*. 2012;126:2935-42.
- Hemo E, Mohr R, Uretzky G, Katz G, Popovits N, Pevni D, et al. Long-term outcomes of patients with diabetes receiving bilateral internal thoracic artery grafts. *J Thorac Cardiovasc Surg*. 2013;146:586-92.
- Puskas JD, Sadiq A, Vassiliades TA, Kilgo PD, Lattouf OM. Bilateral internal thoracic artery grafting is associated with significantly improved long-term survival, even among diabetic patients. *Ann Thorac Surg*. 2012;94:710-5; discussion 5-6.
- Society of Thoracic Surgeons. National Adult Cardiac Surgery Database, Cleveland Clinic Harvest Report, Harvest 1, 2012.
- Puskas JD. Why did you not use both internal thoracic arteries? *Circulation*. 2012;126:2915-7.
- Kieser TM, Rose MS, Aluthman U, Montgomery M, Louie T, Belenkie I. Toward zero: deep sternal wound infection after 1001 consecutive coronary artery bypass procedures using arterial grafts: implications for diabetic patients. *J Thorac Cardiovasc Surg*. February 11, 2014 [Epub ahead of print].
- Deo SV, Shah IK, Dunlay SM, Erwin PJ, Locker C, Altarabsheh SE, et al. Bilateral internal thoracic artery harvest and deep sternal wound infection in diabetic patients. *Ann Thorac Surg*. 2013;95:862-9.
- Buda AJ, Macdonald IL, Anderson MJ, Strauss HD, David TE, Berman ND. Long-term results following coronary bypass operation: importance of preoperative factors and complete revascularization. *J Thorac Cardiovasc Surg*. 1981;82:383-90.
- Jones EL, Craver JM, Guyton RA, Bone DK, Hatcher CR Jr, Riechwald N. Importance of complete revascularization in performance of the coronary bypass operation. *Am J Cardiol*. 1983;51:7-12.
- Bell MR, Gersh BJ, Schaff HV, Holmes DR Jr, Fisher LD, Alderman EL, et al. Effect of completeness of revascularization on long-term outcome of patients with three-vessel disease undergoing coronary artery bypass surgery: a report from the Coronary Artery Surgery Study (CASS) Registry. *Circulation*. 1992;86:446-57.
- Ong AT, Serruys PW. Complete revascularization: coronary artery bypass graft surgery versus percutaneous coronary intervention. *Circulation*. 2006;114:249-55.
- Schwartz L, Bertolet M, Feit F, Fuentes F, Sako EY, Toosi MS, et al. Impact of completeness of revascularization on long-term cardiovascular outcomes in patients with type 2 diabetes mellitus: results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D). *Circ Cardiovasc Interv*. 2012;5:166-73.
- Diegeler A, Borgermann J, Kappert U, Breuer M, Boning A, Ursulescu A, et al. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *N Engl J Med*. 2013;368:1189-98.
- Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med*. 2012;366:1489-97.
- Sabik JF, Blackstone EH, Lytle BW, Houghtaling PL, Gillinov AM, Cosgrove DM. Equivalent midterm outcomes after off-pump and on-pump coronary surgery. *J Thorac Cardiovasc Surg*. 2004;127:142-8.
- Sabik JF, Gillinov AM, Blackstone EH, Vacha C, Houghtaling PL, Navia J, et al. Does off-pump coronary surgery reduce morbidity and mortality? *J Thorac Cardiovasc Surg*. 2002;124:698-707.
- Polomsky M, He X, O'Brien SM, Puskas JD. Outcomes of off-pump versus on-pump coronary artery bypass grafting: impact of preoperative risk. *J Thorac Cardiovasc Surg*. 2013;145:1193-8.
- Keeling WB, Kilgo PD, Puskas ME, Lattouf OM, Guyton RA, et al. Off-pump coronary artery bypass grafting attenuates morbidity and mortality for patients with low and high body mass index. *J Thorac Cardiovasc Surg*. 2013;146:1442-8.
- Puskas JD, Williams WH, O'Donnell R, Patterson RE, Sigman SR, Smith AS, et al. Off-pump and on-pump coronary artery bypass grafting are associated with similar graft patency, myocardial ischemia, and freedom from reintervention: long-term follow-up of a randomized trial. *Ann Thorac Surg*. 2011;91:1836-42; discussion 42-3.
- Puskas JD, Thourani VH, Kilgo P, Cooper W, Vassiliades T, Vega JD, et al. Off-pump coronary artery bypass disproportionately benefits high-risk patients. *Ann Thorac Surg*. 2009;88:1142-7.
- Emmert MY, Salzberg SP, Seifert B, Rodriguez H, Plass A, Hoerstrup SP, et al. Is off-pump superior to conventional coronary artery bypass grafting in diabetic patients with multivessel disease? *Eur J Cardiothorac Surg*. 2011;40:233-9.
- Renner A, Zittermann A, Aboud A, Puhler T, Hakim-Meibodi K, Quester W, et al. Coronary revascularization in diabetic patients: off-pump versus on-pump surgery. *Ann Thorac Surg*. 2013;96:528-34.
- Srinivasan AK, Grayson AD, Fabri BM. On-pump versus off-pump coronary artery bypass grafting in diabetic patients: a propensity score analysis. *Ann Thorac Surg*. 2004;78:1604-9.
- Magee MJ, Dewey TM, Acuff T, Edgerton JR, Hebel JF, Prince SL, et al. Influence of diabetes on mortality and morbidity: off-pump coronary artery bypass grafting versus coronary artery bypass grafting with cardiopulmonary bypass. *Ann Thorac Surg*. 2001;72:776-80; discussion 80-1.

Discussion

Dr John G. Byrne (Boston, Mass). No disclosures. This report adds to the considerable work our colleagues at Cleveland Clinic have contributed to the idea that bilateral internal mammary arteries (BIMAs) are preferable in most CABG patients, even in those with diabetes, and that although the use of BIMAs in patients

with diabetes comes at the expense of increased DSWI, it is worth it in terms of survival. I have 4 questions.

Although you found that factors such as female sex, large BMI, peripheral vascular disease, and so forth contributed to DSWI, you also state that it is in these very patients for whom BIMA is most preferable. So does that mean now that at the Cleveland Clinic your practice has changed? Do you recommend BIMAs for every single patient, even those who are massively obese, who perhaps have undergone radiotherapy, or have chronic obstructive pulmonary disease, emergencies, and so forth?

Dr Raza. Thank you, Dr Byrne, for the question. We believe that the therapy should be patient oriented and individualized. If a patient has a higher risk of developing DSWI, such as a massively obese woman, it is very unlikely that she would undergo bilateral ITA grafting electively at Cleveland Clinic. Thus, we recommend the use of bilateral ITA grafts for those patients for whom the risk of developing DSWI is low.

Dr Byrne. What I am wondering about is some sort of scoring system. Perhaps the next report at next year's The American Association for Thoracic Surgery might have a scoring system that could indicate, for instance, if this patient's score is low enough, that patient should undergo BIMA.

Dr Raza. That is an interesting idea.

Dr Byrne. Second question. You must have a glucose control protocol, such as a Portland type protocol.

Dr Raza. That is a great point. We do have a strict glucose monitoring protocol by which every patient's glucose is monitored closely in the perioperative period, and every effort is made to keep the glucose <160 mg/dL. Also, if a patient has uncontrolled diabetes and blood glucose levels are high, if time allows, we suggest achieving control of those levels before surgery is performed. That is perhaps one of the reasons that when we studied the effect of the HbA1c levels on the risk of developing DSWI, our data did not show any significant association.

Dr Byrne. What was the distribution of your BIMA grafts, to the left side, to the right side? Do you have any data to share with us on that? What is the Cleveland Clinic's preference and what is your practice?

Dr Raza. Of the right ITA?

Dr Byrne. Do you put it to the right side, the left side?

Dr Raza. Most right ITA grafts went to left-sided lesions, and nearly one quarter in our data set went to right-sided lesions. We believe that the right ITA should go to the second most important coronary artery, which is usually the circumflex. If we use a right ITA graft to the right coronary artery, we would see whether it is totally occluded or critically stenosed, say, >90%.

Dr Byrne. Thank you. Finally, you recommend in your report that you should skeletonize the left internal mammary artery to both mammary arteries and that this is mandatory for this notion, this concept, this practice pattern. Most of us, of course, use pedicle grafts. What happens when you use a pedicle graft? Also, what happens if the right internal mammary artery does not reach the target? Do you use it as a free graft, a T graft and so forth?

Dr Raza. That is a great point. If the target is distal, usually the right ITA is used as a free graft off the left ITA. That allows us to graft more vessels, and that is the usual practice at Cleveland Clinic and our preference.

Could you please repeat the second question?

Dr Byrne. The skeletonization.

Dr Raza. Sternal wound infection is the Achilles heel of bilateral ITA grafting, and the skeletonized approach has been shown to be associated with a decreased risk of sternal wound infections. Thus, we recommend and use a skeletonized approach for ITA harvest.

Dr Harold L. Lazar (*Boston, Mass*). I have no conflicts to report. I have 1 question about your long-term outcomes. Many patients who do receive a single internal mammary usually have a higher risk profile. Thus, can you tell us as far as the long-term deaths, what percentage were cardiac related versus noncardiac related and did they differ between the groups of bilateral and single mammary disease?

Dr Raza. Regarding the risk profile, the patients who were good candidates for bilateral ITA grafting were those with a lower BMI and good control of their blood glucose levels. We were aware that the patient characteristics might have influenced our findings, and, therefore, we adjusted for them. Our adjusted results showed that bilateral ITA grafting was associated with a 21% decrease in late mortality. So, we did adjust for the effects of all available patient characteristics.

Dr Lazar. But do you know, were the deaths cardiac related or noncardiac related in the long term?

Dr Raza. Sorry, the long-term survival?

Dr Lazar. The incidence of deaths for long-term survival, was there a difference between cardiac-related deaths versus noncardiac?

Dr Raza. We used the Social Security Death Master File for long-term follow-up. It takes into account all-cause mortality, but does not distinguish between cardiac-related and noncardiac-related death. Thus, the long-term survival in our study was just based on all-cause mortality.

Dr Antonio Laudito (*Duluth, Minn*). I thank you for continuing with your group to show the data, the reality. I am a little bit surprised when you look at the STS database that the use of the bilateral mammary artery, instead of increasing is decreasing. I was wondering if you have any idea of the reason? Of course, it is an ironical question. But it is interesting to see what happens always with your data in the past when you show the difference clearly between vein, a single mammary. The curve did not diverge when you showed, in a very excellent way, the difference. The curve diverged when the left internal mammary artery received a diagnosis-related group number.

Dr Raza. That is a great point. As you mentioned, we have shown that bilateral ITA grafting is associated with improved long-term survival compared with single ITA grafting. However, the reason it has not been widely adopted is, as I mentioned, that sternal wound infection is its Achilles heel. In recent years at our center, the risk of sternal wound infection has decreased because of several approaches we have adopted, including the use of perioperative prophylactic antibiotics and achieving control of the blood glucose levels before going to surgery, if time allows. The skeletonized approach for ITA harvest is another method that we use to decrease the risk of sternal wound infections. If these approaches are used, the risk of sternal wound infections can be lowered, making bilateral ITA grafting more likely to be adopted.

Dr Laudito. We have also to stop to be politically correct saying that a BIMA operation is not the usual coronary operation, occurred more times, more clinical experience, more surgical experience. It is not the usual CABG. So we need to have the appreciation and the time for that.

Thank you.

Dr Raza. Thank you for your comments.

Dr Saswata Deb (*Toronto, Ontario, Canada*). A very nice talk. High-grade target vessel stenosis is an important issue for radials. Did you consider that for mammary arteries, especially the right?

Dr Raza. Nearly 1200 patients in our data set underwent radial artery grafting. However, it was not within the scope of this project to specifically consider the outcomes of patients undergoing radial

artery grafting or the issue of high-grade target vessel stenosis. Our usual practice is to use radial artery grafts to fill in the left-sided gaps. A radial graft can go to the right coronary artery, but only if it is totally occluded or the stenosis is >90%.

Dr Deb. My question was more for the right ITA. High-grade stenosis, was that factor considered for where the right ITA was going to be placed?

Dr Raza. Regarding right ITA grafting, we believe that it should go to the second most important coronary artery, which is usually the circumflex. Competitive flow, which you are getting at, becomes more of an issue when we graft the vessel to the right coronary artery. Thus, if we use the right ITA to graft the right coronary artery, we would first have determined whether it is totally occluded or critically stenosed, that is, >90%.

EDITORIAL COMMENTARY

Two internal thoracic arteries really are better

Andrea J. Carpenter, MD, PhD

The research reported by Raza and colleagues presents compelling evidence that best outcomes of surgical revascularization in persons with diabetes are achieved with the use of bilateral internal thoracic artery grafts and complete revascularization with only modest increase in deep sternal wound infection. It is time for greater adoption of bilateral internal thoracic artery grafting across coronary surgery centers.

Raza and colleagues¹ are to be congratulated on an elegant review of operative strategies that may improve or hinder outcomes of coronary revascularization in patients with diabetes. Mining the extensive outcomes database maintained at the Cleveland Clinic, they identified the optimal strategy for long-term survival among patients with diabetes to include use of bilateral internal thoracic arteries (BITAs) and achievement of complete revascularization. In their cohort with diabetes only 2 complications occurred more frequently with the use of BITA: reoperation for bleeding and deep sternal wound infection (DSWI).

Almost all practicing cardiac surgeons believe that completeness of revascularization is important to good outcomes. However, the adoption of BITA use has been extremely slow, with surgeons avoiding BITA in the presence of diabetes, obesity, and chronic obstructive pulmonary disease because of concern regarding DSWI. This opinion persists in our culture despite a wealth of literature supporting the benefit of BITA on survival, symptom relief, and diminished repeat revascularization.

Although Dr Sabik has long been a proponent of BITA for coronary grafting, there were only 938 cases (8%) using BITA in this cohort of 11,922 patients with diabetes.¹ The rate of DSWI was statistically elevated compared with patients receiving a single internal thoracic artery graft, but the influence of DSWI on survival was small. Evaluating patient factors associated with DSWI revealed that women with body mass index > 30, peripheral artery disease, prior myocardial infarction, and pharmacologic therapy for diabetes were at highest risk. Men, nonobese women, and all patients with diet-controlled diabetes had very modest increased risk.

Acknowledging that the report by Raza and colleagues is a retrospective review and that the total number of patients having BITA was only 8% of the cohort,¹ these data still provide compelling evidence that the risk of excess DSWI with BITA grafting is small. Although the adverse effects of DSWI can be severe, the overall long-term survival is still better with BITA.

From the University of Texas Health Science Center, San Antonio, TX.

Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Aug 29, 2014; revisions received Aug 29, 2014; accepted for publication Aug 31, 2014.

Address for reprints: Andrea Carpenter, MD, PhD, University of Texas Health Science Center, San Antonio, TX (E-mail: carpentera2@uthscsa.edu).

J Thorac Cardiovasc Surg 2014;148:1266-7

0022-5223/\$36.00

Copyright © 2014 by The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2014.08.039>

APPENDIX E1. VARIABLES CONSIDERED IN MULTIVARIABLE ANALYSES**Demographic Data**

Age (y), sex, race, weight (kg), height (cm), weight/height ratio, body surface area (m²), body mass index (kg/m²).

Acuity

New York Heart Association functional class (I-IV), emergency surgery.

Cardiac Comorbidity

Previous myocardial infarction, atrial fibrillation/flutter, complete heart block or pacer, heart failure.

Noncardiac Comorbidity

Treated diabetes, insulin-treated diabetes (from 1990), non-insulin-treated diabetes (from 1990), diet-controlled diabetes, peripheral arterial disease, carotid disease, hypertension, history of smoking, previous stroke, bilirubin (mg/dL), cholesterol (mg/dL), triglycerides (mg/dL), creatinine (mg/dL).

Coronary Anatomy

Number of systems diseased ($\geq 50\%$ stenosis), left main disease (0%, $\geq 70\%$, and $\geq 50\%$ stenosis), left anterior

descending system disease (0%, $\geq 70\%$, and $\geq 50\%$ stenosis), left circumflex system disease (0%, $\geq 70\%$, and $\geq 50\%$ stenosis), right coronary artery system disease (0%, $\geq 70\%$, and $\geq 50\%$ stenosis).

Procedure

Insertion of assist device, surgeon.

Procedure: Coronary Artery Bypass Grafting Detail

Number of internal thoracic artery (ITA) grafts used (none, 1, 2), complete revascularization, conduit (arterial grafts, only arterial grafts, gastroepiploic or inferior epigastric artery, ITA, free ITA, in situ ITA, left ITA, right ITA, other, radial artery, saphenous vein graft), graft location (left anterior descending, left anterior descending diagonals, left circumflex territory, right coronary artery territory).

Support

Cardiopulmonary bypass (off-pump vs on-pump).

Experience

Date of operation (years since January 1, 1972).

FIGURE E1. Probability of developing a deep sternal wound infection (*DSWI*). *Solid line* represents parametric estimate enclosed within a 68% confidence limit band. This graph represents a nomogram of the logistic regression equation for *DSWI* (Table 1). A, Effect of body mass index. Simulation was based on pharmacologically treated (non–insulin-treated) diabetic woman with no previous myocardial infarction or history of peripheral arterial disease undergoing coronary artery bypass grafting with cardiopulmonary bypass and bilateral internal thoracic artery grafts, receiving complete revascularization, and treated in 2007. B, Effect of date of operation. Simulation was based on pharmacologically treated (non–insulin-treated) diabetic woman with no previous myocardial infarction or history of peripheral arterial disease, body mass index of 29 kg/m², undergoing coronary artery bypass grafting with cardiopulmonary bypass, grafting with bilateral internal thoracic artery grafts, and complete revascularization.

FIGURE E2. Survival of diabetic patients who underwent coronary artery bypass grafting estimated using the Kaplan-Meier method. A, Stratified by deep sternal wound infection (*DSWI*) and bilateral (*BITA*) and single (*SITA*) internal thoracic artery grafting. B, Stratified by *BITA* and *SITA* grafting and showing the effect of *DSWI* on survival.

FIGURE E3. Cumulative distribution of predicted 10-year survival. A, For a combination of surgical techniques. The increasing order of these cumulative distributions of 10-year survival from left to right is shown in the table underneath the graph. B, For the number of ITA grafts used. C, For complete versus incomplete revascularization. D, For off-pump versus on-pump coronary artery bypass grafting. *ITA*, Internal thoracic artery; *BITA*, bilateral ITA graft; *SITA*, single ITA graft; *SVG*, saphenous vein graft.

FIGURE E4. Patient factors associated with maximum survival benefit from best combination of surgical techniques (ie, bilateral internal thoracic artery grafting, complete revascularization, and off-pump surgery). *Solid line* represents parametric estimate enclosed within a 68% confidence limit band. This graph represents a nomogram of the logistic regression equation for maximum survival benefit (Table 3). A, Older age. Simulation is based on pharmacologically (non-insulin) treated diabetic woman presenting with mild symptoms of heart failure (New York Heart Association class II), cholesterol level 230 mg/dL, bilirubin 0.63 mg/dL, no history of heart failure or peripheral arterial disease, undergoing nonemergency surgery. B, Lower cholesterol. Simulation is based on a 60-year-old pharmacologically (non-insulin) treated diabetic woman presenting with mild symptoms of heart failure (New York Heart Association class II), bilirubin 0.63 mg/dL, no history of heart failure or peripheral arterial disease, undergoing nonemergency surgery. C, Lower bilirubin. Simulation is based on a 60-year-old pharmacologically (non-insulin) treated diabetic woman presenting with mild symptoms of heart failure (New York Heart Association class II), cholesterol level 230 mg/dL, no history of heart failure or peripheral arterial disease, undergoing nonemergency surgery.

ACD

TABLE E1. Patient characteristics and surgical details

Variable	n*	Mean ± SD or No. (%)
Demographic data		
Age (y)	11,922	62 ± 9.8
Female sex	11,922	3388 (28)
Race		
White	11,362	9789 (86)
Black	11,362	640 (5.6)
Other	11,362	933 (8.2)
Weight (kg)	9849	86 ± 18
Height (cm)	9847	170 ± 10
BMI (kg/m ²)	9838	30 ± 5.7
Acuity		
NYHA functional class	11,869	
I		2009 (17)
II		4584 (39)
III		1645 (14)
IV		3631 (31)
Emergency surgery	11,921	277 (2.3)
Cardiac comorbidity		
Previous MI	11,922	6736 (57)
Atrial fibrillation/flutter	10,231	180 (1.8)
Complete heart block or pacer	10,231	87 (0.85)
Ventricular arrhythmia	6533	415 (6.4)
Heart failure	11,922	1866 (16)
Coronary artery disease†		
Left main	10,695	2007 (19)
LAD system	11,370	10,733 (94)
LCx system	11,293	9124 (81)
RCA system	11,294	9805 (87)
No. of diseased systems	11,407	
0		81 (0.71)
1		762 (6.7)
2		2792 (24)
3		7772 (68)
Noncardiac comorbidity		
Diabetes		
Diet controlled		1687 (14)
Pharmacologically treated		10,234 (86)
Non-insulin treated		3766 (32)
Insulin treated		2743 (23)
Latest preoperative HbA1c	2541	7.8 ± 1.7
PAD	11,922	1995 (17)
Previous stroke	11,922	959 (8.1)
Carotid disease	11,922	2476 (21)
Hypertension	7337	5928 (81)
Renal dialysis	4495	108 (2.4)
Creatinine (mg/dL)	7142	1.3 ± 1.2
Creatinine clearance (Cockcroft-Gault)	6539	85 ± 41
Glomerular filtration rate‡	7172	72 ± 31
Blood urea nitrogen (mg/dL)	7139	22 ± 12
Cholesterol (mg/dL)		
Total	8591	210 ± 60
High-density lipoprotein	5871	39 ± 12
Low-density lipoprotein	4781	114 ± 46

(Continued)

TABLE E1. Continued

Variable	n*	Mean ± SD or No. (%)
Bilirubin (mg/dL)	6386	0.6 ± 0.5
Triglycerides (mg/dL)	7678	202 ± 172
Hematocrit (%)	6626	38 ± 5.5
Procedure		
No. of ITA grafts	11,922	
0§		2518 (21)
1		8466 (71)
2		938 (7.9)
Conduit: saphenous vein	11,922	11,110 (93)
SVG only	11,922	2491 (21)
Conduit: radial artery	11,922	1258 (11)
Incomplete revascularization†	11,922	2109 (18)

SD, Standard deviation; BMI, body mass index; NYHA, New York Heart Association; MI, myocardial infarction; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; HbA1c, hemoglobin A1c; PAD, peripheral arterial disease; ITA, internal thoracic artery; SVG, saphenous vein graft. *Patients with data available. †Stenosis ≥ 50%. ‡Modification of Diet in Renal Disease formula. §SVG only in 99%.

TABLE E2. Unadjusted in-hospital outcomes

Outcomes	BITA (n = 938)	SITA (n = 8466)	P value	Off-pump (n = 602)	On-pump (n = 11,320)	P value	Incomplete revascularization (n = 2109)	Complete revascularization (n = 9813)	P value
Mortality	7 (0.75)	105 (1.2)	.19	7 (1.2)	219 (1.9)	.18	47 (2.2)	179 (1.8)	.2
DSWI	32 (3.4)	181 (2.1)	.01	8 (1.3)	250 (2.2)	.15	42 (2.0)	216 (2.2)	.6
Stroke	9 (0.96)	148 (1.7)	.07	8 (1.3)	244 (2.2)	.17	52 (2.5)	200 (2.0)	.2
Renal failure	18 (1.9)	343 (4.1)	.001	46 (7.6)	400 (3.5)	<.0001	72 (3.4)	374 (3.8)	.4
Ventilation >24 h	9 (4.0)	228 (11)	.001	28 (11)	231 (11)	>.9	25 (13)	234 (11)	.5
Postoperative LOS >14 d	56 (6.0)	691 (8.2)	.02	49 (8.1)	1041 (9.2)	.4	193 (9.2)	897 (9.1)	>.9
Reoperation for bleeding	41 (4.4)	256 (3.0)	.03	16 (2.7)	385 (3.4)	.3	65 (3.1)	336 (3.4)	.4

Data presented as No. (%). BITA, Bilateral internal thoracic artery grafting; SITA, single internal thoracic artery grafting; DSWI, deep sternal wound infection; LOS, length of stay.

TABLE E3. Risk factors for in-hospital death

Factor	Estimate ± SE	P value	Reliability (%)*
Demographic data			
Female sex	0.61 ± 0.14	<.0001	95
Older age†	0.52 ± 0.11	<.0001	88
Acuity			
NYHA functional class			90
II	−0.77 ± 0.21	.0002	
III-IV	−0.38 ± 0.17	.02	
Emergency surgery	1.98 ± 0.20	<.0001	100
Cardiac comorbidity			
Previous MI	0.55 ± 0.15	.0003	80
Higher number of coronary systems diseased (≥50% stenosis)	0.31 ± 0.13	.01	50
Noncardiac comorbidity			
Diabetes			36‡
Pharmacologically treated	0.24 ± 0.24	.3	
Insulin treated	0.19 ± 0.18	.3	
PAD	0.56 ± 0.16	.0003	83
Procedure			
ITA graft			81
Single (vs SVG only)	−0.95 ± 0.17	<.0001	
Bilateral (vs SVG only)	−0.98 ± 0.42	.02	
Bilateral vs single§	−0.18 ± 0.43	.7	
Incomplete revascularization (vs complete)	−0.037 ± 0.18	.8	3.4‡
Off-pump surgery (vs on-pump)	−0.34 ± 0.41	.4	2.4‡
Earlier date of operation	−0.0085 ± 0.01	.4	79

C-statistic = 0.79. SE, Standard error; NYHA, New York Heart Association; MI, myocardial infarction; PAD, peripheral arterial disease; ITA, internal thoracic artery; SVG, saphenous vein graft. *Percentage of times the factor appeared in 500 bootstrap models. †Exp(age/50), exponential transformation. ‡Variables were forced into the model, even though the reliability was low. §Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. ||Date of operation (years since January 1, 1972).

TABLE E4. Risk factors for stroke

Factor	Estimate ± SE	P value	Reliability (%)*
Demographic data			
Female sex	0.44 ± 0.14	.001	51
Older age†	0.55 ± 0.10	<.0001	100
Acuity			
NYHA functional class III-IV	0.29 ± 0.14	.03	62
Emergency surgery	1.2 ± 0.24	<.0001	99
Cardiac comorbidity			
LCx system disease‡	0.71 ± 0.29	.02	67
Noncardiac comorbidity			
Diabetes			64
Pharmacologically treated	0.51 ± 0.23	.03	
Insulin treated	−0.08 ± 0.18	.7	
Higher creatinine	0.11 ± 0.043	.01	67
Procedure			
ITA graft			23§
Single (vs SVG only)	−0.37 ± 0.16	.02	
Bilateral (vs SVG only)	−0.56 ± 0.37	.10	
Bilateral vs single	−0.15 ± 0.35	.7	
Incomplete revascularization (vs complete)	−0.01 ± 0.17	>.9	2.8§
Off-pump surgery (vs on-pump)	−0.33 ± 0.37	.4	16§
Earlier date of operation¶	−0.02 ± 0.0094	.07	69

C-statistic = 0.71. SE, Standard error; NYHA, New York Heart Association; LCx, left circumflex coronary artery; ITA, internal thoracic artery; SVG, saphenous vein graft. *Percentage of times the factor appeared in 500 bootstrap models. †Exp(age/50), exponential transformation. ‡Stenosis > 0%. §Variables were forced into the model, even though the reliability was low. ||Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. ¶Date of operation (years since January 1, 1972).

TABLE E5. Risk factors for reoperation for bleeding

Factor	Estimate ± SE	P value	Reliability (%) [*]
Demographic data			
BMI [†]	1.19 ± 0.18	<.0001	89
Acuity			
Emergency surgery	0.64 ± 0.26	.01	100
Cardiac comorbidity			
2-System disease [‡]	−0.44 ± 0.14	.001	82
Noncardiac comorbidity			
Diabetes			30 [§]
Pharmacologically treated	0.076 ± 0.15	.6	
Insulin treated	0.0049 ± 0.15	>.9	
History of smoking	−0.27 ± 0.11	.01	62
Procedure			
ITA graft			91
Single (vs SVG only)	0.081 ± 0.14	.6	
Bilateral (vs SVG only)	0.48 ± 0.20	.02	
Bilateral vs single	0.38 ± 0.18	.03	
Incomplete revascularization (vs complete)	−0.27 ± 0.14	.06	25 [§]
Off-pump surgery (vs on-pump)	0.15 ± 0.27	.6	7.4 [§]
Earlier date of operation [¶]	−0.3 ± 0.0068	<.0001	95

C-statistic = 0.66. SE, Standard error; BMI, body mass index; ITA, internal thoracic artery graft; SVG, saphenous vein graft. ^{*}Percentage of times the factor appeared in 500 bootstrap models. [†](25/BMI)², inverse squared transformation. [‡]Stenosis ≥ 50%. [§]Variables were forced into the model, even though the reliability was low. ^{||}Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. [¶]Date of operation (years since January 1, 1972).

TABLE E6. Risk factors for prolonged length of stay (>14 days)

Factor	Estimate ± SE	P value	Reliability (%) [*]
Demographic data			
Female sex	0.43 ± 0.073	<.0001	96
Older age [†]	0.38 ± 0.053	<.0001	100
BMI [‡]	0.12 ± 0.052	.02	67
Race: black or other (vs white)	0.21 ± 0.097	.03	58
Acuity			
NYHA functional class			89
II	−0.30 ± 0.098	.002	
III-IV	−0.0007 ± 0.091	>.9	
Emergency surgery	1.23 ± 0.15	<.0001	100
Cardiac comorbidity			
Complete heart block or pacer	0.61 ± 0.28	.03	54
Heart failure	0.46 ± 0.081	<.0001	99
Graft location (LCx territory)	0.34 ± 0.10	.0009	79
Noncardiac comorbidity			
Diabetes			96
Pharmacologically treated	0.31 ± 0.11	.005	
Insulin treated	0.041 ± 0.084	.6	
PAD	0.52 ± 0.077	<.0001	100
Previous stroke	0.58 ± 0.099	<.0001	99
Higher creatinine	0.34 ± 0.062	<.0001	99
Lower cholesterol [§]	−0.37 ± 0.14	.02	96
Procedure			
ITA graft			97
Single (vs SVG only)	−0.34 ± 0.087	<.0001	
Bilateral (vs SVG only)	−0.22 ± 0.17	.2	
Bilateral vs single	0.053 ± 0.16	.7	
Incomplete revascularization (vs complete)	0.0018 ± 0.093	>.9	12 [¶]
Off-pump surgery (vs on-pump)	−0.27 ± 0.16	.10	35 [¶]
Earlier date of operation [#]	−0.001 ± 0.006	.9	31 [¶]

C-statistic = 0.70. SE, Standard error; BMI, body mass index; NYHA, New York Heart Association; LCx, left circumflex coronary artery; PAD, peripheral arterial disease; ITA, internal thoracic artery; SVG, saphenous vein graft. ^{*}Percentage of times the factor appeared in 500 bootstrap models. [†]Exp(age/50), exponential transformation. [‡](BMI/25)², squared transformation. [§]Log(preoperative cholesterol), logarithmic transformation. ^{||}Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. [¶]Variables were forced into the model, even though the reliability was low. [#]Date of operation (years since January 1, 1972).

TABLE E7. Risk factors for renal failure (n = 11,814*)

Factor	Estimate ± SE	P value	Reliability (%)†
Demographic data			
Female sex	0.36 ± 0.11	.001	94
Race: black or other (vs white)	0.38 ± 0.13	.004	79
Acuity			
NYHA functional class III-IV	0.50 ± 0.11	<.0001	56
Emergency surgery	1.56 ± 0.21	<.0001	100
Cardiac comorbidity			
Heart failure	0.62 ± 0.11	<.0001	94
LCx system disease‡	0.47 ± 0.16	.003	65
Noncardiac comorbidity			
Diabetes			77
Pharmacologically treated	0.26 ± 0.18	.16	
Insulin treated	0.11 ± 0.11	.3	
PAD	0.42 ± 0.12	.0003	65
Carotid disease	0.39 ± 0.11	.0005	84
Higher creatinine§	1.24 ± 0.087	<.0001	100
Procedure			
ITA graft			62
Single (vs SVG only)	−0.034 ± 0.16	.8	
Bilateral (vs SVG only)	−0.39 ± 0.29	.18	
Bilateral vs single	−0.37 ± 0.25	.14	
Incomplete revascularization (vs complete)	−0.02 ± 0.14	.9	3.6¶
Off-pump surgery (vs on-pump)	0.19 ± 0.18	.3	11¶
More recent date of operation#	0.11 ± 0.008	<.0001	100

C-statistic = 0.76. SE, Standard error; NYHA, New York Heart Association; LCx, left circumflex coronary artery; PAD, peripheral arterial disease; ITA, internal thoracic artery; SVG, saphenous vein graft. *Patients with preoperative renal failure (n = 108) were removed from the denominator. †Percentage of times the factor appeared in 500 bootstrap models. ‡Stenosis ≥ 50%. §Log(preoperative creatinine), logarithmic transformation. ||Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. ¶Variables were forced into the model, even though the reliability was low. #Date of operation (years since January 1, 1972).

TABLE E8. Risk factors for prolonged ventilation (>24 hours; n = 2272*)

Factor	Estimate ± SE	P value	Reliability (%)†
Demographic data			
BMI‡	0.28 ± 0.81	.0005	94
Acuity			
NYHA functional class III-IV	0.71 ± 0.15	<.0001	88
Emergency surgery	1.69 ± 0.41	<.0001	97
Cardiac comorbidity			
Previous MI	0.81 ± 0.16	<.0001	94
Left main disease§	0.61 ± 0.15	<.0001	98
Noncardiac comorbidity			
Diabetes			12
Pharmacologically treated	−0.075 ± 0.26	.8	
Insulin treated	−0.029 ± 0.15	.8	
Carotid disease	0.48 ± 0.16	.002	55
Higher creatinine¶	0.58 ± 0.12	<.0001	83
Lower cholesterol#	0.12 ± 0.05	.02	67
Procedure			
ITA graft			79
Single (vs SVG only)	−1.25 ± 0.31	<.0001	
Bilateral (vs SVG only)	−1.95 ± 0.46	<.0001	
Bilateral vs single**	−0.73 ± 0.36	.04	
Incomplete revascularization (vs complete)	−0.091 ± 0.25	.7	2.4
Off-pump surgery (vs on-pump)	−0.15 ± 0.23	.5	7.4
More recent date of operation††	0.10 ± 0.031	.002	67

C-statistic = 0.73. SE, Standard error; BMI, body mass index; NYHA, New York Heart Association; MI, myocardial infarction; ITA, internal thoracic artery; SVG, saphenous vein graft. *Prolonged ventilation data were available beginning January 2002. †Percentage of times the factor appeared in 500 bootstrap models. ‡(BMI/25)², squared transformation. §Stenosis ≥ 50%. ||Variables were forced into the model, even though the reliability was low. ¶Log(preoperative creatinine), logarithmic transformation. # (230/Preoperative cholesterol), inverse squared transformation. **Estimate derived by running the model with the same variables for patients with multivessel coronary artery disease. ††Date of operation (years since January 1, 1972).

TABLE E9. Effect of HbA1c on deep sternal wound infection (n = 2541*)

Factor	Estimate ± SE	P value	Reliability (%)†
Demographic data			
Shorter height‡	2.65 ± 0.79	.0007	71
Noncardiac comorbidity			
Diabetes			42§
Insulin treated	0.63 ± 0.30	.2	
Diet treated	−0.11 ± 0.63	.9	
HbA1c	0.62 ± 0.68	.4	22§
Procedure			
ITA graft			71
Single (vs SVG only)	0.31 ± 1.02	.8	
Bilateral (vs SVG only)	0.46 ± 1.14	.7	
Incomplete revascularization (vs complete)	−0.33 ± 0.53	.5	2.4§
Off-pump surgery (vs on-pump)	−0.53 ± 0.45	.2	28§
Earlier date of operation¶	−0.14 ± 0.047	.004	65

C-statistic = 0.70. *HbA1c*, Hemoglobin A1c; *SE*, standard error; *ITA*, internal thoracic artery; *SVG*, saphenous vein graft. *Number of patients with HbA1c values available for analysis. †Percentage of times the factor appeared in 500 bootstrap models. ‡(180/Height)², inverse squared transformation. §Variables were forced into the model, even though the reliability was low. ||Log(HbA1c), logarithmic transformation. ¶Date of operation (years since January 1, 1972).

TABLE E10. Incremental risk factors for death after CABG: multivessel disease

Risk factor	Coefficient ± SE	P value	Reliability (%)*
Early hazard phase			
Demographic data			
Female sex	0.42 ± 0.10	<.0001	99
Older age†	0.48 ± 0.079	<.0001	100
Acuity			
NYHA functional class			93
II	−0.067 ± 0.019	.0004	
III-IV	0.85 ± 0.22	<.0001	
Emergency surgery	1.43 ± 0.16	<.0001	100
Noncardiac comorbidity			
Diabetes			74
Treated	0.28 ± 0.18	.11	
Insulin-treated	0.20 ± 0.12	.10	
PAD	0.48 ± 0.11	<.0001	84
Previous stroke	0.54 ± 0.14	<.0001	87
Lower cholesterol‡	0.11 ± 0.023	<.0001	59
Higher bilirubin	0.15 ± 0.063	.02	74
Procedure			
Earlier date of operation§	−0.0086 ± 0.0072	.2	24
ITA graft			100
SVG (vs SITA)	0.72 ± 0.12	<.0001	
Bilateral (vs SITA)	−0.53 ± 0.36	.14	
Late hazard phase			
Demographic data			
Female sex	0.095 ± 0.033	.005	75
Older age¶	0.97 ± 0.071	<.0001	100
Cardiac comorbidity			
Heart failure	0.46 ± 0.041	<.0001	100
Noncardiac comorbidity			
Diabetes			100
Treated	0.44 ± 0.05	<.0001	
Insulin treated	0.04 ± 0.042	.4	
PAD	0.41 ± 0.034	<.0001	100
Previous MI	0.11 ± 0.028	.0001	99
Previous stroke	0.28 ± 0.05	<.0001	100
Carotid disease	0.11 ± 0.04	.005	90
Higher creatinine#	0.21 ± 0.10	.11	100
Procedure			
ITA graft			100
SVG (vs SITA)	0.20 ± 0.031	<.0001	
Bilateral (vs SITA)	−0.24 ± 0.063	.0001	

SE, Standard error; *NYHA*, New York Heart Association; *PAD*, peripheral arterial disease; *ITA*, internal thoracic artery; *SVG*, saphenous vein graft; *SITA*, single internal thoracic artery; *PAD*, peripheral arterial disease; *MI*, myocardial infarction. *Percentage of times the factor appeared in 500 bootstrap models. †Exp(age/50), exponential transformation. ‡(1/Cholesterol)², inverse squared transformation. §Date of operation (years since January 1, 1972). ||Variables were forced into the model, even though the reliability was low. ¶(50/Age)², inverse squared transformation. #Log(creatinine), logarithmic transformation.