Impact of prior intracoronary stenting on late outcomes of coronary artery bypass surgery in diabetics with triple-vessel disease

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ABSTRACT

Objective: Recent studies have indicated that coronary artery bypass grafting (CABG) outcomes in patients with prior stents are suboptimal. We aimed to study the impact of prior percutaneous coronary intervention (PCI) with stenting (PCI-S) on late CABG mortality in diabetic patients with triple-vessel disease.

Methods: We reviewed the primary nonemergency CABG experience from a single U.S. institution (n = 7005; 1996-2007, Toledo, Ohio). Diabetics with triple-vessel disease (n = 1583) were identified and divided into 2 groups: (1) prior PCI-S (n = 202); and (2) no prior PCI (No-PCI [n = 1381]). Hierarchic Cox proportional hazards models were used to assess the effect of prior PCI-S on 5-year mortality after CABG. A propensity score for PCI-S and No-PCI patients was derived using a nonparsimonious logistic regression and used to generate a 1:1 (PCI-S to No-PCI) matched cohort.

Results: In model 1, after adjusting for preoperative clinical characteristics, medications, off-pump surgery, and isolated CABG surgery status, prior PCI-S was associated with a 39% increased risk of mortality (hazard ratio [HR] = 1.39, with 95% confidence interval [CI; 1.02, 1.90]; $P = .04$). Further adjustment for date of surgery (model 2) (HR = 1.39, with 95% CI [1.02, 1.91]; $P = .04$) or operative parameters (model 3) (HR = 1.38, with 95% CI [1.01, 1.88]; $P = .046$) did not alter the association. The 1:1 matched-cohort analysis confirmed the increased risk associated with PCI-S (HR = 1.61, with 95% CI [1.03, 2.51]; $P = .037$).

Conclusions: Patients who have both diabetes and triple-vessel disease, and have undergone prior PCI-S, have poorer long-term outcomes after CABG compared with those who have had no prior PCI-S. (J Thorac Cardiovasc Surg 2015;149:1302-9)

Comparison five-year Kaplan-Meier survival for 1:1 propensity matched prior PCI status groups.

Central Message

Diabetic triple-vessel disease patients with prior percutaneous coronary intervention with stent placement (PCI-S) have poorer long-term outcomes following CABG compared to patients with no prior PCI-S.

Perspective

We found prior PCI with intracoronary stenting to be associated with increased long-term mortality following primary CABG in triple-vessel diabetics. An early team-based approach including a cardiologist and cardiac surgeon should be implemented for optimal revascularization strategy selection in diabetics with triple-vessel disease and for close medical follow-up of those higher risk CABG patients with history of intracoronary stents. This may improve clinical decision-making in a high-risk CAD population arguably at most need for optimal medical management and intervention. Future investigation is needed to elucidate whether these findings derive from the underlying disease characteristics, implanted stents, or both.

See Editorial Commentary page 1310.

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
CI	= confidence interval
DES	= drug-eluting stents
HR	= hazard ratio
ICD	= International Classification of Diseases
PCI	= percutaneous coronary intervention
PCI-S	= PCI with stenting

The past decade has witnessed a surge in percutaneous coronary intervention (PCI) as a primary modality for coronary revascularization, driven in large part by its less-invasive nature compared with coronary artery bypass grafting (CABG). A recent national analysis reporting revascularization trends from 2001 to 2008 noted a steadily decreasing rate of CABG surgery in the face of a stable PCI rate, which is increasingly based on drug-eluting stents (DES).¹ Furthermore, the rate of multivessel stenting remained fairly constant, at approximately 12% of annual PCI-stenting (PCI-S) procedures.² Since the introduction of DES, PCI-S has been extended increasingly to high-risk patient groups, including those who have diabetes and those who have multivessel and left main coronary artery disease (CAD). Consequently, more patients with a prior history of PCI-S treatment of their CAD are being referred for CABG.

A possible adverse effect of prior PCI-S on early outcomes after CABG surgery has been described.^{3,4} This effect has been attributed in part to the increased bleeding risk and perioperative stent thrombosis that results from an imperfect balance of perioperative anticoagulation.⁵ Improved understanding of perioperative anticoagulation and optimal timing of surgery after PCI-S may decrease the rate of perioperative complications, with some reports suggesting no early adverse effects.^{6,7}

How the long-term outcomes of patients after primary CABG may be affected by the presence of in situ stents has not been as thoroughly investigated.^{6,8-12} Recent reports have postulated that such patients have increased inflammation and endothelial injury,¹³⁻¹⁷ and that the grafts in those who have undergone CABG and have pre-existing intracoronary stents may have suboptimal placement and patency.¹⁸ We hypothesized that in diabetic patients with triple-vessel disease, a history of PCI with stent placement portends poorer long-term survival, given the established endothelial dysfunction in diabetic patients^{19,20} and the significant CAD burden associated with triple-vessel disease. We leveraged the availability of a real-world cardiac surgery registry with late-mortality follow-up, to assess the impact of prior stenting on 5-year all-cause mortality in patients who undergo primary CABG.

METHODS**Study Design and Data Collection**

This study is a retrospective analysis of a prospectively collected cardiac surgery database surveying the CABG experience (n = 7005) of a single cardiac surgical team (Mercy Saint Vincent Medical Center, Toledo, Ohio) from January 1996 till March 2007. Data collection and reporting is in accordance with The Society of Thoracic Surgeons National Adult Cardiac Database definitions and criteria.²¹ Patients who had undergone CABG with concomitant surgery for cardiac valvular or aortic disease were excluded. For the purposes of this study, inclusion was restricted to primary CABG patients who had both diabetes (n = 2555; 36.5%) and triple-vessel disease (n = 5248; 74.9%). Triple-vessel disease was defined as $\geq 50\%$ stenosis in all 3 native coronary vessels, or left main artery plus right CAD.

A total of 1868 (26.7%) patients with triple-vessel disease had diabetes as well. Of these, 285 (15.3%) were excluded from the analysis for 1 or more reasons: having repeat CABG (n = 111), having emergency (n = 90) or salvage (n = 8) surgery, and/or being a nonemergency patient with a preoperative intra-aortic balloon pump and/or cardiogenic shock (n = 87). Patients with a history of having PCI before CABG were included only if the PCI entailed stenting, regardless of stent type. The final study population consisting of 1583 patients was divided into 2 comparison groups based on prior intra-coronary stenting status: (1) 202 (12.8%) with prior stents (PCI-S); and (2) 1381 (87.2%) with no prior PCI (No-PCI). The institutional review board approved the study. Informed consent was waived, based on the fact that the study is a deidentified retrospective analysis.

Outcome Measures

The primary endpoint was all-cause mortality. Long-term survival data were obtained from our service follow-up, and the U.S. Social Security Death Index database, and verified by cross-checking with the Ohio State Death Registry. Early mortality was defined as death within 30 days of CABG surgery or during the index hospitalization for surgery. Long-term follow-up was assessed at 5 years, with 30 patients (1.9%) lost to follow-up over this time period. Lastly, cause-specific mortality data were extracted from death certificates in the Ohio State Death Registry using International Classification of Diseases (ICD) -9 (1996-1998) and -10 (1999 onward) revision codes. Cause of death was known for 282 of 345 (81.7%) mortality events. Cardiac mortality was defined by ICD-10 codes I00 to I09, I11, I13, and I20 to I51, and their corresponding ICD-9 codes: 390 to 398, 402, 404, and 410 to 429. Coronary heart disease mortality was identified²² using ICD-10 codes I20 to I25 and their corresponding ICD-9 codes, 410 to 414 and 429.2.

Statistical Analysis

Descriptive statistics for categorical variables are summarized as frequency (%) and compared among the prior PCI-S and No-PCI groups, using Pearson χ^2 analysis or the Fisher exact test, as appropriate. Continuous parameters are presented as mean $\pm$ SD, or as median (interquartile range), and compared using the unpaired Student *t* test or the nonparametric Wilcoxon rank sum test. Ejection fraction data were missing for 326 of 7005 (4.7%) patients in the database who had undergone CABG (49 of 1583 [3.1%] for the current analysis); these missing data were handled by multiple imputation.

Univariable and multivariable logistic regression were used to assess the effect of PCI-S on early mortality. The Kaplan-Meier survival method with the log-rank significance test was used to compare 5-year survival between the 2 groups, for the baseline population as well as in the propensity-matched subcohort. To determine the risk-adjusted effect of prior PCI-S on 5-year mortality, 3 hierarchic adjusted Cox proportional hazards models were constructed.

Model 1 included all preoperative clinical variables in Table 1, medications, off-pump versus on-pump surgery, and isolated CABG surgery status. Model 2, in addition to model 1, adjusted for year of

TABLE 1. Patient baseline characteristics according to PCI status group in overall and matched cohort

Preoperative characteristics	Whole cohort			Matched cohort		
	PCI-S (n = 202)	No-PCI (n = 1381)	Standard difference (%)	PCI-S (n = 195)	No-PCI (n = 195)	Standard difference (%)
Age (y; mean $\pm$ SD)*	63.0 $\pm$ 10.4	65.0 $\pm$ 9.6	20.0	63.6 $\pm$ 10.1	62.8 $\pm$ 9.5	8.2
Gender, male	129 (63.9)	871 (63.1)	1.7	125 (64.1)	122 (62.6)	3.1
Body mass index (kg/m ²)						
<30	95 (47.0)	631 (45.7)	2.6	93 (47.7)	83 (42.6)	10.3
30-35	55 (27.2)	435 (31.5)	9.5	55 (28.2)	56 (28.7)	1.1
>35	52 (25.8)	315 (22.8)	7.0	47 (24.1)	56 (28.7)	10.4
Congestive heart failure	36 (17.8)	258 (18.7)	2.3	36 (18.5)	34 (17.4)	2.9
NYHA class						
I	12 (5.9)	111 (8.0)	8.3	12 (6.2)	12 (6.2)	0.0
II	41 (20.3)	248 (18.0)	5.8	39 (20)	39 (20)	0.0
III	90 (44.6)	635 (46.0)	2.8	87 (44.6)	87 (44.6)	0.0
IV	59 (29.2)	387 (28.0)	2.7	57 (29.2)	57 (29.2)	0.0
Ejection fraction (mean % $\pm$ SD)	46.6 $\pm$ 11.5	47.5 $\pm$ 11.2	0.9	46.7 $\pm$ 11.7	46.2 $\pm$ 11.9	0.6
Hypertension	181 (89.6)	1232 (89.2)	1.3	176 (90.3)	180 (92.3)	7.1
Hypercholesterolemia*	165 (81.7)	1023 (74.1)	18.4	158 (81)	164 (84.1)	8.2
Smoking status						
Current smoker	44 (21.8)	265 (19.2)	6.4	42 (21.5)	38 (19.5)	5.0
Former smoker	94 (46.5)	582 (42.1)	8.9	89 (45.6)	93 (47.7)	4.2
Nonsmoker	64 (31.7)	534 (38.7)	14.7	64 (32.8)	64 (32.8)	0.0
Left main disease	33 (16.3)	243 (17.6)	3.5	32 (16.4)	38 (19.5)	8.1
Myocardial infarction*	155 (76.7)	740 (53.6)	50.0	148 (75.9)	147 (75.4)	1.2
Unstable angina	56 (27.7)	363 (26.3)	3.2	54 (27.7)	47 (24.1)	8.2
Family history of CAD	129 (63.9)	894 (64.7)	1.7	125 (64.1)	136 (69.7)	11.9
Renal failure	14 (6.9)	87 (6.3)	2.4	14 (7.2)	15 (7.7)	1.9
Arrhythmia	22 (10.9)	168 (12.2)	4.1	22 (11.3)	21 (10.8)	1.6
Chronic lung disease	41 (20.3)	289 (20.9)	1.5	39 (20)	38 (19.5)	1.3
Cerebrovascular disease	51 (25.3)	406 (29.4)	9.2	49 (25.1)	38 (19.5)	13.5
Peripheral vascular disease	44 (21.8)	281 (20.4)	3.4	44 (22.6)	40 (20.5)	5.1
Preoperative medications						
Insulin	76 (37.6)	473 (34.3)	6.9	72 (36.9)	76 (39.0)	4.3
Antiplatelet drugs	136 (67.3)	979 (70.9)	7.8	131 (67.2)	125 (64.1)	6.5
Beta-blockers	128 (63.4)	813 (58.9)	9.2	125 (64.1)	129 (66.2)	4.4
Digoxin	15 (7.4)	142 (10.3)	10.2	15 (7.7)	14 (7.2)	1.9
Diuretics	54 (26.7)	349 (25.3)	3.2	53 (27.2)	51 (26.2)	2.3
Operative characteristics						
Isolated CABG	179 (88.6)	1174 (85.0)	10.7	172 (88.2)	178 (91.3)	10.2
Off-pump surgery	6 (3.0)	39 (2.8)	1.2	6 (3.1)	5 (2.6)	3.0
Year of CABG surgery*						
1996-1997	8 (4.0)	225 (16.3)	41.6	8 (4.1)	15 (7.7)	15.3
1998-1999	21 (10.4)	225 (16.3)	17.4	21 (10.8)	19 (9.7)	3.6
2000-2001	43 (21.3)	235 (17.0)	10.9	43 (22.1)	38 (19.5)	6.4
2002-2003	57 (28.2)	294 (21.3)	16	53 (27.2)	52 (26.7)	1.1
2004-2005	41 (20.3)	280 (20.3)	0	41 (21.0)	48 (24.6)	8.6
2006-2007	32 (15.8)	122 (8.8)	21.4	29 (14.9)	23 (11.8)	9.1

Values are n (%), unless otherwise indicated. Arrhythmia indicates atrial fibrillation, heart block, or resuscitated cardiac arrest. *PCI-S*, Percutaneous coronary intervention, with stenting; *PCI*, percutaneous coronary intervention; *NYHA*, New York Heart Association; *CAD*, coronary artery disease; *CABG*, coronary artery bypass grafting; *SD*, standard deviation. * $P < .05$ for comparison of PCI-S and No PCI in overall cohort. No statistically significant differences were found in the matched cohort.

CABG surgery. Model 3 adjusted, in addition to model 1, for operative characteristics. The proportional hazard assumption was tested by using the log(-negative-log[Survival{t}]) plot, in addition to testing the “group $\times$ time” interaction term. The Breslow method was used to handle event ties. In addition, interaction with stent-type era (before and after U.S. Food and Drug Administration approval of DES, in April 2003) was tested.

Lastly, we calculated a propensity score for PCI-S and No-PCI patients, using a nonparsimonious logistic regression including all covariates in model 2. Poststratification for stent-type era, greedy 1:1 propensity-matched PCI-S and No-PCI pairs were derived, using a customized computer algorithm. The greedy 1:1 matching algorithm determined individually for each case the “best” match, based on the propensity score, to within $\pm 1\%$. Matching adequacy of patient factors was

TABLE 2. Other operative characteristics according to PCI status group

Operative characteristics	All (N = 1583)	PCI-S (n = 202)	No-PCI (n = 1381)	P value
Number of arterial grafts				.98
0	31 (2.0)	4 (2.0)	27 (2.0)	
1	810 (51.2)	106 (52.4)	704 (51.0)	
2	667 (42.1)	83 (41.1)	584 (42.3)	
3	75 (4.7)	9 (4.5)	66 (4.8)	
Total number of graft anastomoses (mean ± SD)	3.6 ± 0.9	3.6 ± 0.8	3.6 ± 0.9	.90
ITA	1541 (97.4)	196 (97.0)	1345 (97.4)	.76
Radial	733 (46.3)	91 (45.1)	642 (46.5)	.70
Perfusion time (min)*	88.2 ± 29.7	87.4 ± 36.8	88.3 ± 28.6	.73
Crossclamp time (min)*	56.0 ± 21.2	54.4 ± 21.2	56.2 ± 21.2	.25

Values are n (%), unless otherwise indicated. P value reflects comparison between PCI-S and No-PCI groups. PCI, Percutaneous coronary intervention; PCI-S, percutaneous coronary intervention, with stenting; ITA, internal thoracic artery; SD, standard deviation. *Data on 1538 patients with on-pump surgery.

assessed by calculating the standardized percent difference,²³ in addition to between-groups statistical comparisons of all patient factors. Two-sided probability values were calculated. All analyses were done using Stata 12 (Stata Corporation, College Station, Tex).

RESULTS

The study population included 1583 patients with diabetes and triple-vessel disease who underwent primary CABG, of whom 202 (12.8%) had ≥1 prior PCI with stents deployed. Preoperative clinical characteristics according to PCI status are presented in Table 1. Compared with the No-PCI group, PCI-S patients were younger and more had previous history of myocardial infarction and hypercholesterolemia. The 2 groups had no differences in preoperative medication use (Table 1). In addition, operative characteristics were similar between the 2 groups. No differences were found in the number or type of arterial grafts received, the total number of graft anastomoses, or the relative frequency of off-pump surgery (Tables 1 and 2).

Of 1583 patients, 52 (3.3%) died within thirty days of the surgery or during the index hospitalization for the

surgery: 6 (3.0%) patients in the PCI-S group, and 46 (3.3%) in the No-PCI group (P = .79). In multivariable logistic regression adjusting for 18 preoperative clinical variables (Table 1), in addition to preoperative medication, off-pump surgery, isolated CABG surgery status, and date of CABG surgery, prior PCI-S was not an independent predictor of early mortality (odds ratio = 0.89, with 95% confidence interval [CI] [0.36, 2.22]; P = .81).

Five-year cumulative survival was 78.5% (95% CI [76.3%, 80.6%]) and 74.8% (95% CI [68.2%, 80.3%]) for the No-PCI and PCI-S groups, respectively (log-rank test, P = .23) (Figure 1). Using a multivariable Cox proportional hazards model and after adjusting for 18 preoperative clinical variables (Table 1), preoperative medication, off-pump surgery, and isolated CABG surgery status, PCI-S was associated with a 39% increased risk of mortality at 5 years (hazard ratio [HR] = 1.39 with 95% CI [1.02, 1.90]; P = .04) (Table 3). Further adjustment for date of CABG surgery (HR = 1.39, with 95% CI [1.02, 1.91]; P = .04), and for operative parameters (HR = 1.38, with 95% CI [1.01, 1.88]; P = .046) did not alter the association (Figure 2). Stent-type era was used as a surrogate for predominant type of stent implanted, given reports in the literature of the rapid and widespread adoption of DES after they were approved by the U.S. Food and Drug Administration. No significant interaction between PCI-S and stent-type era was found (P = .59).

The 1:1 propensity-matched PCI-S and No-PCI subcohorts (n = 390; 195 pairs) were well matched for demographic, risk, and operative factors (Table 1). Five-year cumulative survival was 83.5% (95% CI [77.5%, 88.1%]) and 74.4% (95% CI [67.6%, 80.0%]) for the No-PCI and PCI-S groups, respectively (log-rank test, P = .035) (Figure 3). The Cox proportional hazards model in matched patients confirmed the increased risk associated with PCI-S observed in the overall risk-adjusted analysis (HR = 1.61, with 95% CI [1.03, 2.51]; P = .037) (Figure 2).

Cause-specific 5-year mortality was known for 282 of 345 (81.7%) of the deaths in the overall cohort. Five-year cardiac mortality rates were higher in the group who

FIGURE 1. Five-year Kaplan-Meier survival (all-cause mortality) data compared for prior PCI-status groups, for all patients. Error bars represent 95% confidence intervals. PCI, Percutaneous coronary intervention; PCI-S, percutaneous coronary intervention with stenting.

TABLE 3. Independent preoperative predictors of 5-year all-cause mortality in model 1

	Adjusted hazard ratio (95% CI)	P value
Prior PCI-stent	1.39 (1.02-1.9)	.04
Age (/10 y)	1.53 (1.33-1.76)	<.001
BMI (kg/m ²)		.23
<30	—	—
30-35	0.93 (0.72-1.21)	.59
>35	1.37 (1.02-1.85)	.04
Congestive heart failure	1.42 (1.09-1.85)	.009
Ejection fraction (per 5% increments)	0.93 (0.88-0.97)	.002
Renal failure	2.94 (2.17-3.99)	<.001
Chronic lung disease	1.74 (1.35-2.23)	<.001
Cerebrovascular disease	1.32 (1.04-1.66)	.02
Peripheral vascular disease	1.59 (1.25-2.02)	<.001

Model 1 is adjusted for the 18 preoperative clinical characteristics in Table 1 + preoperative medications + off-pump status + isolated coronary artery bypass grafting status. *CI*, Confidence interval; *PCI*, percutaneous coronary intervention; *BMI*, body mass index.

underwent PCI-S (17 of 202, 8.4%), compared with the No-PCI group (103 of 1381; 7.5%). Notably, 100% of PCI-S cardiac mortality was categorized as being related to coronary heart disease, compared with 89.3% (92 of 103) of No-PCI cardiac mortality (Figure 4, A). Analysis of cause-specific mortality in the matched cohort verified the increased trend of cardiac and coronary heart disease mortality with PCI-S (Figure 4, B).

DISCUSSION

Our analysis of a real-world CABG series of patients with diabetes and triple-vessel disease showed that patients with a prior history of PCI-S had higher 5-year, all-cause

mortality after CABG compared with counterparts who had not received intracoronary stents. Both cardiac and noncardiac mortality rates were higher in the group who had undergone PCI-S, with cardiac mortality being driven mainly by coronary heart disease. We did not find an increase in the secondary endpoint of early mortality among the prior PCI-S group, an observation previously reported.^{6,7} To our knowledge, this study is the first that addresses the potential long-term effects of stents on CABG outcomes in this specific high-risk patient population.

The majority of previous studies, with notable exceptions, reported no impact of prior PCI on mid- or long-term survival in the general population undergoing CABG. Mannacio and colleagues,⁸ in a multicenter study that included 7855 patients referred for primary isolated CABG surgery, reported increased 3-year (odds ratio = 2.2, with 95% CI [1.3, 3.4]; *P* = .001) and 5-year (odds ratio = 1.8, with 95% CI [1.1, 2.8]; *P* = .004) mortality in patients with multiple prior PCI. Chocron and colleagues,⁹ in a secondary analysis of participants in the IMAGINE (Ischaemia Management with Accupril Post-Bypass Graft via Inhibition of the Converting Enzyme) trial (N = 2491), over a median follow-up of 2.95 years, reported a history of PCI as an independent predictor of the occurrence of the primary composite endpoint of major adverse cardiac and cerebrovascular events. Analysis of individual endpoints found that repeat revascularization and unstable angina requiring hospitalization, but not all-cause mortality, was significantly associated with history of PCI.⁹ Tran and colleagues¹⁰ described decreased 2-year, age-adjusted survival after CABG, in diabetic patients with prior PCI.¹⁰ However, after adjusting for other confounders, this difference was no longer significant.

FIGURE 2. Unadjusted and adjusted hazard ratios for 5-year CABG mortality with prior PCI-S. Model 1 is adjusted for 18 preoperative clinical characteristics in Table 1 + preoperative medications + off-pump status + isolated CABG status. Model 2 is adjusted for model 1 factors + year of surgery. Model 3 is adjusted for model 1 factors + operative variables, including internal thoracic artery and radial artery graft use, number of arterial grafts, total number of graft anastomoses, and intraoperative perfusion time. *PCI-S*, Percutaneous coronary intervention, with stenting; *CI*, confidence interval.

FIGURE 3. Five-year Kaplan-Meier survival (all-cause mortality) data compared for prior PCI-status groups; 1:1 matched cohort. Error bars represent 95% confidence intervals. *PCI*, Percutaneous coronary intervention; *PCI-S*, percutaneous coronary intervention, with stenting.

Although longer follow-up outcomes were not reported,¹⁰ these findings are consistent with our results, which show that the difference in survival becomes manifest only after 2 years (Figure 3).

Stevens and colleagues,⁶ in an analysis of an administrative CABG database in Massachusetts (n = 9642), found no increase in long-term follow-up mortality in patients who underwent either recent (<14 days post-PCI) or remote PCI (≥14 days post-PCI). Yap and colleagues,¹¹ looking at 13,184 primary isolated patients who had undergone CABG, over a mean follow-up period of 3.3 years, found no increase in mortality in patients who had PCI before CABG. O'Neal and colleagues,¹² in a study of 13,354 primary isolated elective patients who had undergone CABG, and were followed over a median of 8.1 years, did not find PCI to be an independent predictor of all-cause mortality after primary elective CABG.

In contradistinction to this study, almost all previous studies looking at long-term follow-up after CABG, with prior PCI, focused on the general population undergoing CABG, without a specific analysis of particular aspects of patient subgroups known to be associated with suboptimal outcomes after intracoronary stent placement.²⁴ A myriad of factors have been hypothesized to contribute to the possible direct negative impact of intracoronary stents on CABG outcomes. First, stents in general, and DES in particular, have been found to be associated with endothelial dysfunction, both locally and in distal parts of the coronary system, leading to myocardial ischemia and loss of myocardial substrate.^{13,14}

Second, an increase in local and systemic inflammation, both acute and chronic, has been reported in patients with stent placement.¹⁵⁻¹⁷ Endothelial cell injury, increased medial/adventitial wall strain, decreased shear stress, as well as hypersensitivity, and foreign-body reaction to stents

FIGURE 4. Cause-specific 5-year mortality for prior PCI-status groups: A, all patients; B, 1:1 propensity-matched cohort. *PCI-S*, Percutaneous coronary intervention, with stenting; *PCI*, percutaneous coronary intervention.

have all been implicated in the perpetuation of inflammation and subsequent endothelial dysfunction associated with stents.²⁵ Cytostatic drugs deployed in DES, though effective in ameliorating neo-intimal hyperplasia by blocking medial smooth muscle proliferation, are nonspecific and leave behind a denuded endothelium infiltrated with thrombotic material and chronic inflammatory cells.²⁶ In histologic sections of stented and unstented coronary atherosclerotic lesions, Yoneda and colleagues²⁷ reported higher concentrations of T-lymphocytes and macrophages in DES, compared with bare metal stents and unstented lesions, at 10 months poststenting.

Furthermore, drug-eluting polymer platforms have been incriminated in hypersensitivity reactions to DES that occur long after the eluting drug has gone out of the system.²⁸ Newer specific cytostatic drugs and bio-absorbable polymers may help address these shortcomings, but they still require further testing. In diabetics with an inherently compromised endothelial function¹⁹ and an increased propensity for inflammation,²⁰ the above processes may be magnified.²⁹ Together, increased inflammation and endothelial dysfunction can jeopardize graft patency and negatively affect CABG outcomes, as reported in a recent small study showing a trend toward reduced patency of grafts from the internal thoracic artery to the left anterior descending artery in patients with left anterior descending artery stents.¹⁸

Third, multiple stenting and long stents may impose challenges to the ideal placement of coronary-graft anastomoses, necessitating a default placement of these into native vessels of smaller caliber, affecting run-off and consequently graft patency.³⁰ Fourth, in patients with in situ patent stents, surgeons may opt to implant fewer grafts, which may leave other areas of the vessel that are prone to de novo stenosis unprotected. This situation did not occur in our cohort, in which the number of grafts was equivalent in the PCI-S and No-PCI CABG groups (Table 2). Alternatively, these stented, but not grafted targets will necessarily depend on stent durability, which is arguably lower than that of bypass grafts, in particular arterial grafts.

The granularity of the available data does not permit assessment of which of the aforementioned mechanisms plays the most central role in the increased late mortality in the PCI-S group. This apparent increased late-mortality risk, in patients undergoing primary CABG with prior intracoronary stent treatments, remained unchanged, even after adjustment for operative characteristics, including number and type of grafts used. This finding points to the possible contribution to adverse late outcomes of the other aforementioned factors, such as inflammation, vascular dysfunction, and/or the graft anastomosis site. Yet, we cannot exclude that patients with intracoronary stents represent a special high-risk subgroup with more aggressive coronary artery disease explaining the increased late mortality. That said, in our analysis, we controlled for any imbalance of overall cardiovascular risk between the 2 exposure groups by adjusting for multiple parameters associated with cardiovascular risk and function.

Limitations of this study may be attributed to the nonrandomized observational nature of the study, and the fact that it was conducted at a single institution. In addition, we cannot account fully for the possible increased cardiovascular risk of the PCI-S group, despite adjusting for multiple established cardiovascular risk factors, as well as indicators of cardiac function. Our database did not include sufficient detail regarding the indication for PCI-S; the number, location, and type of stents; the number of PCI procedures; or the time from PCI to CABG. These factors have been implicated to modulate stent effect in previous studies.^{4,6}

In our cohort, PCI-S may have been performed previously for the appropriate clinical indication (acute coronary syndrome, or 1-vessel or 2-vessel, stable CAD, without proximal left anterior descending or left main artery involvement). Thus, our study does not suggest that stents are harmful in general, but rather that a compromise of CABG survival benefit in this high-risk patient population might be mediated by the presence of intracoronary stents. Given reported rates of repeat revascularization as high as 13.7% at 1 year after PCI-S, for stable CAD, in diabetics with multivessel disease,³¹ our findings may inform

practice in cases in which PCI-S may be used unduly as an intervention to avoid surgery in diabetics who have triple-vessel stable CAD.

In an attempt to partly address the impact of the type of stent, we conducted a separate analysis based on stent-type era, ie, before and after introduction of DES. We found no significant difference between the 2 stent eras. We are, however, very cautious in interpreting these findings, as the stent era was used as a surrogate of stent type and may reflect varying practice norms within the 2 eras that could confound the observed results. In addition, data pertaining to diabetes duration and control were not available, given the limitations of a registry database. Finally, cause-specific mortality data were derived from death certificates, rather than by independent adjudication, and cause was unknown for 18.3% of deaths.

In conclusion, to our knowledge, our study is the first to report increased long-term mortality after primary CABG in patients with both diabetes and triple-vessel disease who have a history of prior PCI with intracoronary stenting. An early, team-based approach, including a cardiologist and a cardiac surgeon, should be implemented to achieve optimal revascularization strategy selection for patients who have both diabetes and triple-vessel disease, and for close medical follow-up of those higher-risk patients who undergo CABG and have a history of receiving intracoronary stents. We believe that our study is only hypothesis generating. Future investigation is needed to elucidate whether these findings derive from underlying disease characteristics, implanted stents, or both.

Conflict of Interest Statement

Ameer Kabour reports lecture fees from Astra Zeneca, Pfizer, and Bristol Myers Squibb. All other authors have nothing to disclose with regard to commercial support.

References

1. Epstein AJ, Polsky D, Yang F, Yang L, Groeneveld PW. Coronary revascularization trends in the United States, 2001-2008. *JAMA*. 2011;305:1769-76.
2. Riley RF, Don CW, Powell W, Maynard C, Dean LS. Trends in coronary revascularization in the United States from 2001 to 2009: recent declines in percutaneous coronary intervention volumes. *Circ Cardiovasc Qual Outcomes*. 2011;4:193-7.
3. Thielmann M, Neuhauser M, Knipp S, Kottenberg-Assenmacher E, Marr A, Pizanis N, et al. Prognostic impact of previous percutaneous coronary intervention in patients with diabetes mellitus and triple-vessel disease undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg*. 2007;134:470-6.
4. Massoudy P, Thielmann M, Lehmann N, Marr A, Kleinkamp G, Maleszka A, et al. Impact of prior percutaneous coronary intervention on the outcome of coronary artery bypass surgery: a multicenter analysis. *J Thorac Cardiovasc Surg*. 2009;137:840-5.
5. Kremke M, Tang M, Bak M, Kristensen KL, Hindsholm K, Andreassen JJ, et al. Antiplatelet therapy at the time of coronary artery bypass grafting: a multicentre cohort study. *Eur J Cardiothorac Surg*. 2013;44:e133-40.
6. Stevens LM, Khairy P, Agnihotri AK. Coronary artery bypass grafting after recent or remote percutaneous coronary intervention in the Commonwealth of Massachusetts. *Circ Cardiovasc Interv*. 2010;3:460-7.

7. Boening A, Niemann B, Wiedemann A, Roth P, Bodeker RH, Scheibelhut C, et al. Coronary stenting before coronary artery bypass graft surgery in diabetic patients does not increase the perioperative risk of surgery. *J Thorac Cardiovasc Surg.* 2011;142:e53-7.
8. Mannacio V, Di Tommaso L, De Amicis V, Lucchetti V, Pepino P, Musumeci F, et al. Previous percutaneous coronary interventions increase mortality and morbidity after coronary surgery. *Ann Thorac Surg.* 2012;93:1956-62.
9. Chocron S, Baillot R, Rouleau JL, Warnica WJ, Block P, Johnstone D, et al. Impact of previous percutaneous transluminal coronary angioplasty and/or stenting revascularization on outcomes after surgical revascularization: insights from the imagine study. *Eur Heart J.* 2008;29:673-9.
10. Tran HA, Barnett SD, Hunt SL, Chon A, Ad N. The effect of previous coronary artery stenting on short- and intermediate-term outcome after surgical revascularization in patients with diabetes mellitus. *J Thorac Cardiovasc Surg.* 2009;138:316-23.
11. Yap CH, Yan BP, Akowuah E, Dinh DT, Smith JA, Shardey GC, et al. Does prior percutaneous coronary intervention adversely affect early and mid-term survival after coronary artery surgery? *JACC Cardiovasc Interv.* 2009;2:758-64.
12. O'Neal WT, Efrid JT, Anderson CA, Kindell LC, O'Neal JB, Bruce Ferguson T, et al. The impact of prior percutaneous coronary intervention on long-term survival after coronary artery bypass grafting. *Heart Lung Circ.* 2013;22:940-5.
13. Plass CA, Sabydyusheva-Litschauer I, Bernhart A, Samaha E, Petnehazy O, Szentirmai E, et al. Time course of endothelium-dependent and -independent coronary vasomotor response to coronary balloons and stents. Comparison of plain and drug-eluting balloons and stents. *JACC Cardiovasc Interv.* 2012;5:741-51.
14. Mitsutake Y, Ueno T, Yokoyama S, Sasaki K, Sugi Y, Toyama Y, et al. Coronary endothelial dysfunction distal to stent of first-generation drug-eluting stents. *JACC Cardiovasc Interv.* 2012;5:966-73.
15. Almagor M, Keren A, Banai S. Increased C-reactive protein level after coronary stent implantation in patients with stable coronary artery disease. *Am Heart J.* 2003;145:248-53.
16. Gomes WJ, Giannotti-Filho O, Paez RP, Hossne NA Jr, Catani R, Buffolo E. Coronary artery and myocardial inflammatory reaction induced by intracoronary stent. *Ann Thorac Surg.* 2003;76:1528-32.
17. Gomes WJ, Buffolo E. Coronary stenting and inflammation: implications for further surgical and medical treatment. *Ann Thorac Surg.* 2006;81:1918-25.
18. Kamiya H, Ushijima T, Mukai K, Ikeda C, Ueyama K, Watanabe G. Late patency of the left internal thoracic artery graft in patients with and without previous successful percutaneous transluminal coronary angioplasty. *Interact Cardiovasc Thorac Surg.* 2004;3:110-3.
19. Bohlen HG. Mechanisms for early microvascular injury in obesity and type II diabetes. *Curr Hypertens Rep.* 2004;6:60-5.
20. Garcia C, Feve B, Ferre P, Halimi S, Baizri H, Bordier L, et al. Diabetes and inflammation: fundamental aspects and clinical implications. *Diabetes Metab.* 2010;36:327-38.
21. Society of Thoracic Surgeons Adult Cardiac Surgery Database Training Manual v2.81. Available at: <http://www.sts.org/sts-national-database/database-managers/adult-cardiac-surgery-database/data-collection>. Accessed October 30, 2014.
22. Anderson RN, Minino AM, Hoyert DL, Rosenberg HM. Comparability of cause of death between ICD-9 and ICD-10: preliminary estimates. *Natl Vital Stat Rep.* 2001;49:1-32.
23. Austin P. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat—Simul Comput.* 2009;38:1228-34.
24. 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.
25. Van der Heiden K, Gijzen FJ, Narracott A, Hsiao S, Halliday I, Gunn J, et al. The effects of stenting on shear stress: relevance to endothelial injury and repair. *Cardiovasc Res.* 2013;99:269-75.
26. Inoue T, Croce K, Morooka T, Sakuma M, Node K, Simon DI. Vascular inflammation and repair: implications for re-endothelialization, restenosis, and stent thrombosis. *JACC Cardiovasc Interv.* 2011;4:1057-66.
27. Yoneda S, Abe S, Kanaya T, Oda K, Nishino S, Kageyama M, et al. Late-phase inflammatory response as a feature of in-stent restenosis after drug-eluting stent implantation. *Coron Artery Dis.* 2013;24:368-73.
28. Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the research on adverse drug events and reports (RADAR) project. *J Am Coll Cardiol.* 2006;47:175-81.
29. Llano R, Winsor-Hines D, Patel DB, Seifert PS, Hamamdzcic D, Wilson GJ, et al. Vascular responses to drug-eluting and bare metal stents in diabetic/hypercholesterolemic and nonatherosclerotic porcine coronary arteries. *Circ Cardiovasc Interv.* 2011;4:438-46.
30. Goldman S, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs cooperative study. *J Am Coll Cardiol.* 2004;44:2149-56.
31. Lim JY, Deo SV, Kim WS, Altarabsheh SE, Erwin PJ, Park SJ. Drug-eluting stents versus coronary artery bypass grafting in diabetic patients with multi-vessel disease: a meta-analysis. *Heart Lung Circ.* 2014;23:717-25.