Continuative statin therapy after percutaneous coronary intervention improves outcome in coronary bypass surgery: A propensity score analysis of 2501 patients

Vito Mannacio, MD,[a] Pascal Meier, MD,[b,c] Anita Antignano, MD,[d] Michele Mottola, MD,[a] Luigi Di Tommaso, MD,[a] Francesco Musumeci, MD,[e] and Carlo Vosa, MD[a]

Objectives: A history of percutaneous coronary intervention increases the risk of death and complications of coronary artery bypass grafting. This retrospective multicenter study evaluated the impact of continuative use of statin on postoperative outcomes when subsequent elective coronary artery bypass grafting is required after percutaneous coronary intervention.

Methods: Among 14,575 patients who underwent isolated first-time coronary artery bypass grafting between January 2000 and December 2010, 2501 who had previous percutaneous coronary intervention with stenting and fulfilled inclusion criteria were enrolled. Continuative statin therapy was used in 1528 patients and not used in 973 patients. Logistic multiple regression and propensity score analyses were used to assess the risk-adjusted impact of statin therapy on in-hospital mortality and major adverse cardiac events. The Cox proportional hazards model was constructed to assess the effect of continuative statin therapy on 24-month outcome.

Results: At multivariate analysis, age more than 70 years, 3-vessel or 2-vessel plus left main coronary disease, multivessel percutaneous coronary intervention, ejection fraction 0.40 or less, diabetes mellitus, and logistic European System for Cardiac Operative Risk Evaluation 5 or greater were independent predictors of hospital mortality and major adverse cardiac events. After propensity score matching, conditional logistic regression analysis demonstrated that continuative statin therapy before coronary artery bypass grafting reduced the risk for hospital and 2-year mortality (odds ratio [OR], 0.27; 95% confidence interval [CI], 0.12-0. 57; $P = .004$ and OR, 0.6; 95% CI, 0.36-0.96; $P = .04$, respectively) and major adverse cardiac events (OR, 0.31; 95% CI, 0.18-0.78; $P = .003$ and OR, 0.5; 95% CI, 0.34-0.76; $P = .006$, respectively).

Conclusions: Long-term statin treatment after percutaneous coronary intervention improves early and midterm outcome when surgical revascularization will be required. (J Thorac Cardiovasc Surg 2014;148:1876-83)

See related commentary on pages 1884-6.

Recent studies indicate that 10% to 30% of the patients treated by percutaneous coronary intervention (PCI) for multivessel coronary disease require repeated coronary revascularization because of symptom recurrence and restenosis within 2 to 4 years after primary intervention.[1,2] When a subsequent coronary artery bypass grafting (CABG) is necessary, a history of PCI is associated with a higher incidence of perioperative adverse events.[3-7] Thus, in the setting of these high-risk patients, novel technical and pharmacologic strategies are required.

Recent guidelines suggest antiplatelet therapy for primary and secondary prevention before and after implantation of stents or in surgical patients to improve vein-graft patency after CABG.[8-11] Furthermore, robust evidence supports the early and aggressive therapy with inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase statins to reduce cardiovascular adverse events and repeat revascularization procedures after PCI.[12] In patients undergoing CABG, statin therapy exerts multiple pleiotropic effects associated with reduction of myocardial damage and better surgical results.[13-17] This overall efficacy of statins is reflected in the latest American College of Cardiology/American Heart Association guidelines. However, the effect of statin on postoperative outcome of patients with a history of PCI, subsequently referred to CABG, has not been evaluated until now.

Because of the important clinical implications, this study evaluated the impact of continuative statin treatment on early and midterm cardiac mortality and nonfatal major adverse cardiac events (MACE) in those patients who are finally referred to elective CABG after previous PCI by stenting.

From the Department of Cardiac Surgery,[a] University of Naples Federico II, Naples, Italy; Divisions of Cardiology and Cardiac Surgery,[b] Yale Medical School, New Haven, Conn; Cardiology,[c] University College London Hospital, London, United Kingdom; Department of Cardiology,[d] Azienda Ospedaliera Santobono-Pausillipon, Naples, Italy; and Department of Cardiac Surgery,[e] Azienda Ospedaliera S. Camillo Forlanini, Rome, Italy.

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Address for reprints: Vito Mannacio, MD, Via S. Domenico 62, 80127 Naples, Italy (E-mail: vitomannacio2@libero.it).

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CI = confidence interval
CPB = cardiopulmonary bypass
MACE = major adverse cardiac events
MI = myocardial infarction
NO = nitric oxide
OR = odds ratio
PCI = percutaneous coronary intervention

PATIENTS AND METHODS

The study was a retrospective multicenter cohort study designed according to the STROBE statement. Among a total of 14,575 patients who underwent first-time isolated CABG between January 2000 and February 2010, 2051 consecutive patients previously treated by PCI by stenting were evaluated. Additional cardiac procedures and urgent or emergency CABG were exclusion criteria. Patients were classified depending on whether they received (statin group) or did not receive (no statin group) continuous treatment with any kind of statins during the period between PCI and CABG surgery. Types of statin used and the usual dosages were as follows: atorvastatin 20 to 40 mg/d, rosuvastatin 10 to 20 mg/d, simvastatin 20 to 40 mg/d, pravastatin 20 to 40 mg/d, and fluvastatin 20 to 40 mg/d. All patients with suspected low adherence to statin therapy during the last 6 months before CABG were excluded. Adherence to therapy was assessed by rates of prescription refills as reported by Osterberg and Blaschke.[18] We measured statin adherence as the proportion of days covered. We defined patients as being "adherent" if the proportion of days covered was 80% or more. Change from one statin to another was considered adherence with therapy. A total of 1528 patients treated by continuative statin therapy were identified and compared with 973 patients who did not receive continuative statin treatment after PCI. In the statin group, the overall proportion of days covered was 86.4%.

All patients underwent preoperative coronary angiography. Risk stratification was assessed by the logistic European System for Cardiac Operative Risk Evaluation. Low-density lipoprotein levels before the operation were 120 ± 28 mg/dL in the statin group and 159 ± 39 mg/dL in the no statin group ($P < .001$). The main demographic and clinical characteristics of the patients are shown in Table 1.

Troponin I values, assessed preoperatively, and at 8 and 12 hours after operation, and then on every postoperative day until hospital discharge, were collected as markers of myocardial damage. The dose of inotropic support, when required, was considered indicative of postoperative outcome. To avoid bias due to the different duration of follow-up, the last time point for postoperative evaluation was fixed at 24 postoperative months in all patients.

The study protocol was approved by the ethics committee of the University of Naples Federico II. All patients preliminarily granted permission for the use of their medical records for research purposes; thus, individual patient consent was waived for this study.

Perioperative Management

Patients receiving antiplatelet therapy before surgery were managed in accordance with the 2011 American College of Cardiology Foundation/American Heart Association Guideline for Coronary Artery Bypass Graft Surgery.[19] Standardized dual antiplatelet therapy was started when chest tube drainage was less than 20 mL/h.[9] Statins were given 24 hours after surgery and continued over all follow-up time in all patients.[16]

Outcome Measures and Definitions

The end points were (1) hospital mortality and major adverse cardiac events (MACE) and (2) 2-year mortality and MACE.

Hospital mortality was defined as death within 30 days or at any time after operation if the patient did not leave the hospital alive. MACE were defined as a composite end point of nonfatal perioperative myocardial infarction (MI), low output syndrome, significant cardiac arrhythmias, and need for repeat surgical or percutaneous revascularization.

Perioperative acute MI was diagnosed when the criteria indicated by the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction guidelines were fulfilled.[20] Troponin I leakage without electrocardiographic modifications, new loss of viable myocardium, and new regional wall motion abnormality were considered as myocardial damage.[16] Postoperative renal disease was defined as serum creatinine 2.5 mg/dL or greater. Low output syndrome was diagnosed as previously described.[21] High-dose inotropic support was defined when 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or greater of dopamine or any dose of adrenaline was added.

Statistical Analysis

Descriptive statistics were summarized for categoric variables as percentages and compared using the chi-square exact test. Univariate logistic regressions were performed to identify preoperative independent predictors for hospital mortality and MACE based on the preoperative variables mentioned in Table 1. Multivariate logistic regression model included those variables with a probability value of .05 or less for association with at least 1 study end point.

To eliminate confounding bias due to unequal distribution of risk factors among groups, propensity score was performed to generate a subset of matched cases (statin therapy) and controls (no statin therapy) who had the same distribution of covariates. SAS/STAT logistic procedure and a SAS %GMATCH Macro program (SAS Institute Inc, Cary, NC) were used to match cases to controls. Variables listed in Table 1 were used to build a fully adjusted multivariable logistic regression model to compute a propensity score for each patient. The cases were matched with controls to create a 1-to-1 match. Matching was done without replacement, based on caliper matching within a prespecified distance of a maximum of 0.2 of the standard deviation of the logit of the propensity score. If more than 1 control matched equally to 1 case, the control was selected at random.

Comparisons between the 2 groups were performed by the chi-square test to confirm that the 2 groups were successfully matched. The c statistic was 0.89, indicating the good discriminatory power of the propensity model. Hospital mortality and MACE were compared between the 2 matched groups by the 2-tailed McNemar test. Multi-way analysis of variance with correction for serial measurements analyzed troponin I, inotropic support, and postoperative creatinine levels. A Cox proportional hazards model was constructed using the variables reported in Table 1 to evaluate the effect of continuative statin therapy on 24-month survival and MACE. All statistical analyses were performed with the SAS system, version 9.1 (SAS Institute Inc) or SPSS version 13.0 for Windows (SPSS Inc, Chicago, Ill).

RESULTS

All 2501 patients underwent CABG at a median of 38 months (interquartile range, 29-48) after a mean of 1.9 angioplasties by stenting. A total of 1211 patients (48.4%) underwent operation with cardiopulmonary bypass (CPB), and 1290 patients (51.6%) underwent operation off-pump. In patients who underwent on-pump CABG, mean CPB and mean aortic crossclamp times were 83.5 ± 25.2 minutes and 43.2 ± 13.2 minutes,

TABLE 1. Main clinical and demographic characteristics

	Statin group (1528)		No statin group (973)		
	No. of patients	%	No. of patients	%	*P* value
Age ≥70 y	534	35	311	32	.06
Female sex	382	25	272	28	.1
BMI	275	18	205	21	.06
Hypertension	886	58	535	55	.1
Hypercholesterolemia	413	27	370	35	<.001
LDL cholesterol ≥120 mg/dL	395	26	358	37	<.001
Diabetes mellitus	581	38	331	34	.04
Peripheral vascular disease	244	16	116	12	.005
Respiratory disease	367	24	224	23	.6
Renal disease	137	9	78	8	.4
History of MI	718	47	399	41	.003
Ejection fraction ≤40%	245	16	146	15	.5
NYHA class ≥III	580	38	341	35	.1
Logistic euroSCORE ≥5	458	30	253	26	.03
Multivessel coronary disease*	1008	66	613	63	.1
Left main disease	304	20	214	22	.2
Single previous PCI	993	64	678	69	.01
Multiple previous PCI	535	35	295	30	.01
Type of stent					
Bare-metal	688	45	506	52	<.001
Drug-eluting	840	55	467	48	<.001
Indications for CABG					
In-stent restenosis	504	33	294	30	.1
De novo stenosis	456	30	327	33	.6
Combined	539	35	332	35	.8
In-stent thrombosis	29	2	20	2	.9
≥3 grafts/patient	965	63	576	59	.1
Off-pump CABG	792	52	498	51	.8
On-pump CABG	736	48	475	49	.8
Aortic crossclamp time >80 min	271	18	145	15	.7
Therapy					
Dual antiplatelet	1329	87	827	85	.1
Single antiplatelet (ASA)	199	13	146	15	.1
Insulin	81	5	50	5	.9
Oral hypoglycemic	506	33	287	29	.06
β-blockers	1100	72	671	69	.1
Calcium antagonists	488	32	301	31	.6
ACE inhibitors	352	23	204	21	.2

ACE, Angiotensin-converting enzyme; *ASA*, acetylsalicylic acid; *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *LDL*, low-density lipoprotein; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *PCI*, percutaneous coronary intervention.
*Multivessel coronary disease was intended as 3-vessel or 2-vessel plus left main disease.

respectively, without significant differences between groups (86.4 ± 25.3 vs 84.7 ± 30.1, $P = .07$ and 43.8 ± 12.3 vs 41.6 ± 15.2, $P = .06$). As a general rule, on-pump CABG did not result in additional risks for hospital death or MACE compared with off-pump CABG. However, on multivariate analysis of the entire population of patients who underwent on-pump operation, the risk of hospital deaths and MACE was significantly increased in those patients who had a prolonged aortic crossclamp time (>80 minutes) ($P = .01$ and $P = .01$, respectively). In this subpopulation, statin-treated patients had an odds of death 25% (95% CI, 0.25-0.95; $P = .03$) and MACE 30% (95% CI, 0.12-0.8; $P = .03$) lower than in statin-naïve patients.

The number of conduits implanted was 4278 in the statin group and 2530 in the no statin group. The average number of grafts for patient was higher in the statin group (2.8 ± 0.5 vs 2.6 ± 0.6, $P < .001$). The index of completeness (the number of grafts effectively performed on the number of grafts intended at angiography) was similar (0.95 vs 0.94, $P = .8$), as well as the use of the left internal thoracic artery (1473/1528; 96% vs 946/973; 97%, $P = .1$). Other arterial conduits (right internal thoracic artery or radial artery) were used in 65% of patients in the statin group (993/1528) and

TABLE 2. Univariate and multivariate logistic regressions for hospital death

Characteristic	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age ≥70 y	2.5 (1.0-5.3)	.02	2.4 (1.0-4.1)	.04
Female sex	1.5 (0.6-3.5)	.3		
BMI ≥30	2.4 (0.9-6.5)	.07		
Hypertension	3.1 (1.5-6.2)	<.001	2.2 (1.3-4.6)	.008
Hypercholesterolemia	2.8 (1.2-6.7)	.01	1.5 (0.6-3.4)	.09
LDL cholesterol ≥120 mg/dL	1.7 (0.9-3.1)	.05		
Diabetes mellitus	3.1 (1.4-7.1)	.003	2.8 (1.0-5.2)	.02
Peripheral vascular disease	5.4 (1.8-15.3)	.005	3.4 (1.4-9.7)	.02
Respiratory disease	3.4 (1.0-10.8)	.003	2.1 (0.7-7.2)	.08
Renal disease	4.3 (1.1-15.5)	.002	1.6 (0.8-11.1)	.1
History of MI	4.3 (1.9-9.9)	<.001	2.9 (1.5-6.1)	.002
Ejection fraction ≤40%	4.2 (1.4-12.6)	.004	2.1 (1.0-6.7)	.02
NYHA class ≥III	3.3 (1.3-8.1)	.004	2.2 (0.8-5.5)	.09
Logistic euroSCORE ≥5	2.8 (1.3-5.8)	.003	1.3 (1.1-4.1)	.01
Multivessel coronary disease*	2.3 (1.2-4.5)	.008	2.0 (1.1-3.1)	.01
Left main disease ≥50%	1.9 (0.9-4.5)	.1		
Single previous PCI	1.9 (0.8-4.4)	.1		
Multiple previous PCI	3.0 (1.3-6.3)	.004	2.1 (1.1-4.4)	.02
Type of stent				
Bare-metal stent	2.1 (0.9-4.9)	.07		
Drug-eluting stent	2.5 (1.1-5.6)	.01	1.8 (0.6-4.1)	.1
Indications for CABG				
In-stent restenosis	1.1 (0.2-5.5)	.8		
De novo stenosis	2.7 (0.9-8.5)	.7		
Combined	2.2 (0.8-6.5)	.1		
In-stent thrombosis	2.6 (0.7-9.5)	.1		
≥3 grafts/patients	1.8 (0.9-3.4)	.05		
Off-pump CABG	1.7 (0.7-4.2)	.2		
On-pump CABG	2.3 (1.0-4.9)	.02	2.0 (0.8-3.2)	.06
Aortic crossclamp time >80 min	2.4 (1.3-3.9)	.008	2.1 (1.1-3.2)	.01
Postoperative variables				
High-dose inotropic support	2.4 (1.0-5.7)	.03	1.8 (0.7-3.8)	.09
Significant troponin I leakage	1.1 (0.4-2.9)	.9		
Therapy				
Dual antiplatelet	2.0 (0.9-4.2)	.05		
Single antiplatelet (ASA)	2.5 (1.0-6.5)	.03	1.9 (0.6-4.1)	.08
Insulin	2.5 (1.1-5.9)	.04	2.1 (0.7-4.2)	.08
Oral hypoglycemic	1.2 (0.5-1.4)	.8		
β-blockers	1.1 (0.6-1.4)	.7		
Calcium antagonists	1.1 (0.5-1.2)	.8		
ACE inhibitors	1.4 (0.5-2.0)	.9		

ACE, Angiotensin-converting enzyme; *ASA*, acetylsalicylic acid; *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *CI*, confidence interval; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *LDL*, low-density lipoprotein; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *OR*, odds ratio; *PCI*, percutaneous coronary intervention. *Multivessel coronary disease was intended as 3-vessel or 2-vessel plus left main disease.

in 59% of patients in the no statin group (574/973) ($P = .003$).

Total unadjusted hospital mortality was 2.3% (59/2501 patients). Mortality was lower in the statin group (24/1528; 1.5% vs 35/973; 3.3%; $P = .001$). Postoperative MACE occurred more frequently in the no statin group (79/1528; 5.1% vs 76/973; 7.8%, $P = .009$). Univariate and multivariate logistic regression analyses for hospital deaths and MACE revealed several variables as independent predictors for hospital deaths (Table 2) and MACE (Table 3).

In agreement with the concept that preoperative statin therapy protects renal function after coronary surgery, mean serum creatinine levels were significantly increased compared with preoperative values in the no statin group (from 0.82 ± 0.22 to 0.85 ± 0.25, $P = .006$) than in the statin group (from 0.82 ± 0.19 to 0.83 ± 0.23, $P = .2$).

TABLE 3. Univariate and multivariate logistic regressions for major adverse cardiac events

Characteristic	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age ≥70 y	2.3 (1.4-3.7)	<.001	1.8 (1.2-3.3)	.01
Female sex	1.3 (0.8-2.2)	.2		
BMI ≥30	1.0 (0.9-1.9)	.9		
Hypertension	1.8 (1.2-2.8)	.003	1.4 (1.0-2.1)	.03
Hypercholesterolemia	1.6 (1.0-2.7)	.04	1.2 (0.7-2.4)	.07
LDL cholesterol ≥120 mg/dL	1.3 (0.7-2.4)	.2	1.1 (1.0-2.2)	.05
Diabetes mellitus	2.9 (1.8-4.8)	<.001	2.2 (1.3-4.1)	.004
Peripheral vascular disease	3.5 (2.0-6.1)	<.001	2.8 (1.5-4.7)	.002
Respiratory disease	1.4 (0.7-2.7)	.4		
Renal disease	1.6 (0.8-3.3)	.1		
History of MI	2.7 (1.6-4.5)	<.001	1.9 (1.1-3.1)	.008
Ejection fraction ≤40%	2.0 (1.1-3.6)	.01	1.8 (1.0-3.1)	.04
NYHA class ≥III	1.7 (1.0-2.8)	.02	1.4 (0.8-2.1)	.1
Logistic euroSCORE ≥5	2.1 (1.3-3.4)	<.001	1..9 (1.1-3.0)	.007
Multivessel coronary disease*	1.8 (1.2-2.6)	.001	1.4 (1.0-2.3)	.03
Left main disease ≥50%	1.6 (0.9-2.6)	.05		
Single previous PCI	1.4 (0.7-2.7)	.3		
Multiple previous PCI	1.9 (1.2-2.9)	.001	1.6 (0.7-2.4)	.08
Type of stent				
Bare-metal stent	1.4 (0.9-2.2)	.1		
Drug-eluting stent	1.6 (1.0-2.7)	.04	1.4 (0.6-2.1)	.1
Indications for CABG				
In-stent restenosis	1.9 (1.0-3.7)	.03	1.2 (0.5-2.7)	.1
De novo stenosis	1.7 (0.9-3.4)	.1		
Combined	1.3 (0.7-2.5)	.5		
In-stent thrombosis	1.4 (0.6-3.4)	.4		
≥3 grafts/patient	1.4 (1.0-2.1)	.04	1.3 (0.7-1.8)	.1
Off-pump CABG	1.4 (0.8-2.5)	.2		
On-pump CABG	1.6 (1.0-2.4)	.03	1.4 (07-2.1)	.09
Aortic crossclamp time >80 min	1.7 (1.1-2.6)	.004	1.4 (1.0-2.1)	.01
Postoperative variables				
High-dose inotropic support	1.3 (0.7-2.5)	.3		
Significant troponin I leakage	2.1 (1.2-3.8)	.004	1.8 (1.1-3.3)	.009
Therapy				
Dual antiplatelet	1.2 (0.7-2.2)	.3		
Single antiplatelet (ASA)	1.7 (1.0-2.8)	.03	1.4 (0.7-2.1)	.09
Insulin	2.2 (1.3-3.8)	.004	1.9 (1.2-3.1)	.01
Oral hypoglycemic	1.2 (0.6-2.8)	.2		
β-blockers	1.1 (0.5-2.5)	.2		
Calcium antagonists	1.4 (0.8-2.6)	.3		
ACE inhibitors	1.6 (0.7-2.9)	.2		

ACE, Angiotensin-converting enzyme; *ASA*, acetylsalicylic acid; *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *CI*, confidence interval; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *LDL*, low-density lipoprotein; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *OR*, odds ratio; *PCI*, percutaneous coronary intervention. *Multivessel coronary disease was intended as 3-vessel or 2-vessel plus left main disease.

Of note, the subgroup analysis of patients who had been treated by PCI for the left anterior descending artery and patients who had been treated for a coronary artery other than the left anterior descending artery showed no differences in hospital mortality ($P = .7$) and MACE ($P = .4$). Likewise, patients with a history of single PCI had no significant differences between groups in terms of hospital deaths (12/993; 1.2% in the statin group vs 10/678; 1.4% in the no statin group, $P = .8$) or MACE (33/993; 3.3% in the statin group vs 31/678; 4.5% in the no statin group, $P = .2$). By contrast, a significant reduction of hospital deaths and MACE occurred in the statin group when subgroups of patients with a history of multiple PCI were compared (12/535; 2.2% vs 25/295; 8.4%, $P < .001$ and 46/535; 8.4% vs 45/295; 15.2%, $P = .004$).

A high dose of inotropic support postoperatively was required by 152 patients (9.9%) in the statin group versus 144 patients (14.7%) in the no statin group ($P < .001$).

TABLE 4. Main clinical and demographic patient characteristics in subgroups matched on propensity score

	Statin group (931)		No statin group (931)		
	No. of patients	%	No. of patients	%	*P* value
Age ≥70 y	303	32	292	31	.6
Female sex	251	27	257	27	.8
BMI	199	21	191	20	.6
Hypertension	538	58	521	56	.4
Hypercholesterolemia	371	40	361	39	.6
LDL cholesterol ≥120 mg/dL	348	37	351	38	.07
Diabetes mellitus	335	36	331	35	.9
Peripheral vascular disease	123	13	113	12	.8
Respiratory disease	220	24	222	24	.9
Renal disease	85	9	78	8	.6
History of MI	415	44	398	42	.4
Ejection fraction ≤40%	141	15	135	14	.8
NYHA class ≥III	341	36	331	35	.6
Logistic euroSCORE ≥5	245	26	239	25	.8
Multivessel coronary disease*	615	66	601	64	.5
Left main disease	201	22	203	22	.9
Single previous PCI	644	69	650	70	.8
Multiple previous PCI	287	31	281	30	.8
Type of stent					
Bare-metal	469	50	483	52	.5
Drug-eluting	462	50	448	48	.5
Indications for CABG					
In-stent restenosis	279	30	285	30	.9
De novo stenosis	310	33	317	34	.7
Combined	327	35	312	34	.7
In-stent thrombosis	15	2	17	2	.9
≥3 grafts/patient	585	63	550	59	.6
Off-pump CABG	483	52	473	51	.6
On-pump CABG	448	48	458	49	.6
Aortic crossclamp time >80 min	142	15	137	14	.8
Therapy					
Dual antiplatelet					
Single antiplatelet (ASA)	121	13	137	15	.3
Insulin	33	3	36	3	.9
Oral hypoglycemic	288	31	270	29	.4
β-blockers	670	72	670	69	.9
Calcium antagonists	281	30	288	31	.7
ACE inhibitors	216	23	203	22	.5

ACE, Angiotensin-converting enzyme; *ASA*, acetylsalicylic acid; *BMI*, body mass index; *CABG*, coronary artery bypass grafting; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *LDL*, low-density lipoprotein; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *PCI*, percutaneous coronary intervention.
*Multivessel coronary disease was intended as 3-vessel or 2-vessel plus left main disease.

Significant postoperative increases in troponin I values occurred in the no statin group (61.9% vs 37.8%, $P < .001$). Mean postoperative peak value of troponin I was lower in the statin group (0.21 ± 0.18 ng/mL vs 0.42 ± 0.38 ng/mL; $P < .001$). Troponin I levels peaked at 12 hours after the operation in the statin group and at 8 hours in the no statin group.

After propensity score matching, 931 cases were successfully 1:1 matched with 931 corresponding controls (Table 4). After matching, the average number of grafts for patients was similar in both groups (2.72 ± 0.8 vs 2.66 ± 0.5, $P = .05$), as well as the number of left thoracic arteries implanted (914 in the statin group vs 917 in the no statin group, $P = 1$). Other arterial conduits (right internal thoracic artery or radial artery) were used in 63% of the statin group (591/931) and in 59% of the no statin group (550/931) ($P = .06$). Postoperative hospitalization was significantly lower in the statin group (10.2 ± 2.9 days vs 9.2 ± 2.9 days, $P < .001$). Hospital mortality was 1.9% (18 of 931) in the statin group versus 3.7% (35/931) in the no statin group ($P = .02$), and the MACE rate was 5.5% (52/931) versus 9.1% (85/931), respectively ($P = .03$). The McNemar test for paired proportion confirmed significant differences in hospital

TABLE 5. Two-year mortality and major adverse cardiac events in propensity score matched patients analyzed by Cox regression model

Variables	*P* value	Exp	95% CI
Mortality			
Ejection fraction ≤0.40	.004	1.7	1.3-2.9
Multiple previous PCI	<.001	2.4	1.5-3.6
Multivessel coronary disease*	.006	2.1	1.7-2.6
Logistic euroSCORE ≥5	.004	2.3	1.8-3.4
Perioperative troponin I leakage	<.001	3.1	2.1-3.8
No statin therapy before CABG	.002	3.0	2.0-3.6
MACE			
Female sex	.02	1.8	1.2-3.1
Diabetes mellitus	.02	1.9	1.3-3.5
Peripheral vascular disease	.009	2.1	1.4-4.1
Multiple previous PCI	<.001	2.7	1.9-3.9
Logistic euroSCORE ≥5	<.001	2.7	1.8-3.9
Multivessel coronary disease*	.002	2.4	2.1-3.5
Perioperative troponin I leakage	<.001	3.1	2.1-4.5
No statin therapy before CABG	<.001	3.4	2.2-4.6
Single antiplatelet (ASA)	.008	2.1	1.4-3.9

Variables tested: demographic and clinical variables reported in Table 1. *ASA*, Acetylsalicylic acid; *CABG*, coronary artery bypass grafting; *CI*, confidence interval; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *MACE*, major adverse cardiac events; *PCI*, percutaneous coronary intervention. *Multivessel coronary disease was intended as 3-vessel or 2-vessel plus left main disease.

mortality (odds ratio [OR] 2.1; 95% confidence interval [CI], 1.1-3.5; $P = .001$) and MACE (OR, 1.6; 95% CI, 1.1-2.3; $P = .006$). Conditional logistic regression analysis confirmed that continuative statin therapy after previous PCI was significantly associated with reduced risk for hospital mortality (OR, 0.27; 95% CI, 0.12-0.57; $P = .004$) and MACE (OR, 0.31; 95% CI, 0.18-0.78; $P = .003$).

Two-year follow-up was 95% complete for mortality and 88% complete for MACE in the propensity score–matched population. Cardiac deaths and MACE at 2 years were significantly lower in the statin group than in the no statin group (3.4% vs 5.3%, $P = .04$ and 5.5% vs 10.4%, $P = .006$). Conditional logistic regression analysis confirmed that continuative statin therapy after previous PCI was significantly associated with reduced risk for 2-year mortality (OR, 0.6; 95% CI, 0.36-0.96; $P = .04$) and MACE (OR, 0.5; 95% CI, 0.34-0.76; $P = .006$). Moreover, all demographic and clinical variables listed in Table 1 were analyzed by Cox regression model for their effect on 2-year survival and MACE (Table 5).

DISCUSSION

Our results demonstrate that patients with a history of PCI with stenting who were treated by continuative statin therapy before elective primary CABG had a significantly lower risk of operative mortality and MACE and better survival and freedom from MACE at 2 years follow-up compared with untreated patients.

After risk adjustment in a multivariate regression model, age 70 years or more, female sex, ejection fraction 0.40 or less, hypertension, diabetes mellitus, previous MI, 3-vessel or 2-vessel plus left main disease, logistic European System for Cardiac Operative Risk Evaluation 5 or greater, multiple previous PCI, and aortic crossclamp time 80 minutes or more in patients undergoing operation with CPB were independent preoperative markers of deaths and complications. By contrast, the type of stent implanted did not result in significant detrimental effects on hospital mortality and MACE. Of note, perioperative leakage of troponin I was significantly lower in statin-treated patients and was an independent predictor of hospital MACE and 2-year deaths and MACE. This finding is consistent with data from recent literature reporting that an absolute reduction of perioperative troponin I release would translate into a reduction of surgical and overall risk after CABG surgery.[22]

After the statin-treated and untreated patients were balanced by propensity score matching, the benefits conferred by continuative statin therapy on both mortality and MACE were confirmed by an approximately 2-fold risk reduction.

The exact mechanisms underlying these results are unclear and cannot be elucidated from this study. It is likely that statin pleiotropic properties could attenuate the chronic inflammation and focal trauma secondary to PCI, both of which play an important role in the evolution of coronary artery disease.[23-26] This hypothesis is supported by Laufs and coworkers,[27] who demonstrated that statins enhance endothelial nitric oxide (NO) production by directly upregulating endothelial cell NO synthase expression and activity. Thus, by reversing the inhibitory effects of oxidized low-density lipoprotein on endothelial cell NO synthase expression, statins may increase the availability of endothelium-derived NO, which is known to provide the stabilization of the endothelial function and the optimization of local flow.[27] Finally, it is noteworthy that patients in the statin group displayed a slight, but statistically significant prolonged interval of time from PCI to CABG surgery.

Study Limitations

The retrospective nature of the analysis represents the main limitation of this study. Nevertheless, despite the use of propensity scoring and multivariate regression models, immeasurable or unknown factors of bias may still exist. The study also could be limited because of the lack of available cardiac catheterization data at the time of PCI, which hampered the evaluation of coronary lesions and the completeness of percutaneous revascularization, both of which are important determinants of outcome after PCI. Moreover, we could not comment on whether the type of stent used had some impact on outcome because different devices with different characteristics

and indications were implanted in patients over time. Finally, we cannot discuss the specific effectiveness of each statin because different types of statins were used at variable doses and the types of statins were changed in a number of patients between PCI and subsequent CABG.

CONCLUSIONS

Our results demonstrate a substantial improvement in outcome for statin-treated patients who required subsequent CABG surgery after PCI. This study may provide further evidence in the ongoing discussion of beneficial effects of statin and supports a more extensive use of statins, not only in hyperlipidemic patients, as a long-term treatment after PCI. It is regrettable that although statins are indicated by current guidelines, they are underused in daily practice and long-term adherence to drug regimens is generally poor. Our results suggest careful statin treatment after PCI to fully benefit from the potential of these agents in terms of delayed necessity of repeat surgical revascularization and better outcome when surgical revascularization is required.

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