Long-Term Follow Up of Percutaneous Coronary Intervention of Coronary Artery Disease in Women ≤45 Years of Age

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The aim of the present study was to report the short- and long-term clinical outcomes of percutaneous coronary intervention in young women with premature coronary artery disease. From February 2003 to December 2011, 168 consecutive women aged ≤45 years who underwent percutaneous coronary intervention with stent implantation were retrospectively analyzed. The primary end point was the incidence of major adverse cardiac events (MACEs) at short- and long-term follow-up. The mean age was 40.3 ± 2.0 years. Conventional coronary artery disease risk factors were common. Autoimmune or connective tissue diseases were present in 6.5% of the population, 4% had gynecologic diseases, 4 were postpartum, and 9 were taking contraceptives. The left anterior descending coronary artery was the most commonly affected vessel (83.3%) and the most common target vessel for stenting (76.8%). A total of 268 stents were implanted, 95.3% of which were drug-eluting stents. During the hospital stay, 1 patient died, and the incidence of MACEs was 1.2%. No additional events had occurred at 30-day follow-up. After a median follow-up duration of 36 months (interquartile range 12 to 60), cumulate MACE-free survival was 80.5%, the rate of target vessel revascularization was 16.5%, and the rate of stent thrombosis was 3.6%. Cox regression showed that hypertension, smoking, a left ventricular ejection fraction <50%, anterior myocardial infarction, and autoimmune disease were independent predictors of MACEs. In conclusion, percutaneous coronary intervention in young women tends to result in an increased rate of target vessel revascularization during long-term follow-up, which may be influenced by conventional and nonconventional risk factors. **© 2013 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2013;112:918−922)**

Data have shown an increase in the coronary death rate among young women, more prominent than in young men. This is due to steady increases of a spectrum of unfavorable coronary risk factors, such as obesity, diabetes mellitus, hypertension, and metabolic syndrome.[1,2] Previous studies have reported that the prognosis of young patients who undergo percutaneous coronary intervention (PCI) is good.[3,4] However, the numbers of young women in these studies have been limited. In some young women with coronary artery disease (CAD), the underlying pathophysiology is not atherosclerotic, and the risk factors and clinical characteristics in this subset of patients are not equivalent to traditional CAD.[5] However, the impact of PCI on the clinical outcomes of young women with CAD has rarely been investigated. Thus, the aim of this study was to report short- and long-term clinical outcomes in a consecutive series of young women with CAD who underwent PCI with stent implantation.

Methods

One hundred sixty-eight consecutive female patients aged 20 to 45 years who underwent PCI and bare-metal stent or drug-eluting stent (DES) implantation for CAD were included from a large cardiac catheterization registry with a yearly volume of 4,000 to 8,000 PCIs from February 2003 to December 2011. CAD was diagnosed if a stenosis >70% was found in a major epicardial coronary artery.

Conventional risk factors included obesity, smoking, hypertension, hyperlipidemia, and diabetes mellitus. Triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels were assessed without interruption of previous medical therapy, including lipid-lowering drugs. Hyperlipidemia was defined as total cholesterol >200 mg/dl, low-density lipoprotein cholesterol >130 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, or triglyceride >150 mg/dl.[6] The height and weight of each patient were measured at the time of admission, and body mass index was calculated. A body mass index of 18.5 to 24.9 kg/m^2 was considered normal, a body mass index of 25 to 30 kg/m^2 was considered overweight, and a body mass index >30 kg/m^2 was considered obese.[7] Fasting blood glucose levels were obtained within the first 72 hours of hospitalization. Diabetes mellitus was diagnosed by a fasting blood glucose level >125 mg/dl (7.0 mmol/L), a random plasma glucose level >200 mg/dl (11.1 mmol/L), or a history of diabetes mellitus, including those treated with diet control, oral medications, or insulin.[8] Hypertension was diagnosed

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Table 1
Baseline clinical characteristics (n = 168)

Characteristic	Value
Age (yrs)	40.3 ± 2.0
Hypertension	81 (51.6%)
Low-density lipoprotein >130 mg/dl	29 (17.3%)
High-density lipoprotein <40 mg/dl	83 (49.4%)
Triglyceride >150 mg/dl	56 (33.3%)
Diabetes	50 (31.8%)
Family history of early CAD	17 (10.8%)
Smoker	8 (4.8%)
Overweight (body mass index 25−30 kg/m^2)	69 (43.9%)
Obese (body mass index >30 kg/m^2)	17 (10.8%)
Autoimmune disease*	11 (6.5%)
Gynecologic disease	6 (3.6%)
Postpartum	4 (2.4%)
Contraceptives taking	9 (5.4%)
Menopause	0
Old acute MI	8 (4.7%)
Previous CABG	2 (1.2%)
Previous PCI	10 (6.0%)
Clinical presentation	
Non−ST-segment elevation MI	11 (6.5%)
Anterior MI	22 (13.1%)
Inferior MI	21 (12.5%)
Unstable angina pectoris	86 (51.2%)
Chronic renal failure	3 (1.8%)
Chronic heart failure	5 (2.97%)
Left ventricular ejection fraction <50%	9 (5.7%)

Data are expressed as mean ± SD or number (percentage).

* Autoimmune diseases included rheumatic arthritis and Sjögren's syndrome (n = 2), Takayasu's arteritis (n = 4), systemic lupus erythematosus (n = 1), Graves' disease (n = 1), thymoma (n = 1), myositis (n = 1), and membranous nephropathy (n = 1).

Table 2
Coronary angiographic and clinical characteristics (n = 168)

Characteristic	Value
Single-vessel disease	117 (69.6%)
Triple-vessel disease	18 (10.7%)
Diseased coronary artery	
Left main	13 (7.7%)
Left anterior descending	140 (83.3%)
Left circumflex	42 (25%)
Right	50 (29.8%)
Spontaneous coronary dissection	3 (1.7%)
Average number of treated vessels	1.3 ± 0.5
Stented coronary artery	
Left main	10 (6%)
Left anterior descending	129 (76.8%)
Left circumflex	32 (19%)
Right	42 (25%)
Bifurcation stent	5 (3%)
Average number of stents per vessel	1.5 ± 1.0
Average stent length per vessel (mm)	27.8 ± 14.1
Bare-metal stents	12 (4.4%)
DES	256 (95.6%)

Data are expressed as number (percentage) or mean ± SD.

if blood pressure averaged (>3 values) >140/90 mm Hg during admission or if a previous diagnosis of hypertension had been made.

Table 3
Incidence of adverse events during hospital, short-term (30 days and 1 year), and long-term (median 3 years) follow-up

Event	In Hospital	30 Days	1 Year	Long Term
MACEs	2 (1.2%)	2 (1.2%)	18 (10.7%)	32 (19%)
Death	1 (0.6%)	1 (0.6%)	3 (1.8%)	4 (2.4%)
Acute MI	2 (1.2%)	2 (1.2%)	3 (1.8%)	7 (4.2%)
Non−ST-segment elevation MI	2 (1.2%)	2 (1.2%)	2 (1.2%)	3 (1.8%)
ST-segment elevation MI	0	0	1 (0.6%)	4 (2.4%)
Target lesion revascularization	1 (0.6%)	1 (0.6%)	14 (8.3%)	22 (13.2%)
TVR	1 (0.6%)	1 (0.6%)	17 (10.1%)	28 (16.7%)
Repeat PCI	1 (0.6%)	1 (0.6%)	13 (7.8%)	21 (12.5%)
Repeat CABG	0 (0)	0 (0)	4 (2.4%)	7 (4.2%)
Stent thrombosis	2 (1.2%)	2 (1.2%)	3 (1.8%)	6 (3.6%)

Family history was defined as premature coronary heart disease at <55 years of age in a male and <65 years of age in a female first-degree relative, respectively. Smoking was defined as current or former smoking (quit >1 month before the onset of disease). Patients who had stopped smoking >2 years before the onset of disease were classified as nonsmokers.

No patient was excluded from the analysis. All patients provided written informed consent, and the ethics committee approved the database. All patients were advised to continue lifelong aspirin 100 mg/day and clopidogrel 75 mg/day for ≥12 months if appropriate.

All available inpatient and outpatient medical records were reviewed. Information regarding the clinical status at the latest clinical follow-up available was collected by clinical visits and telephone interviews.

The primary end point of our study was the incidence of major adverse cardiac events (MACEs), including cardiac death, myocardial infarction (MI), and target vessel revascularization (TVR; repeat PCI or coronary artery bypass grafting [CABG]) at immediate (in-hospital), short-term (30 days and 1 year), and long-term (median 3 years) follow-up.

Cardiac death was defined as any death from a cardiac cause (e.g., MI, low-output heart failure, fatal arrhythmia), procedure-related death, and death from an unknown cause. Target lesion revascularization was defined as any repeat intervention or CABG of the target lesion. The target lesion was defined as the treated segment 5 mm proximal to the stent and 5 mm distal to the stent. TVR was defined as any repeat intervention or CABG of any segment of the target vessel. The target vessel was defined as the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches, including the target lesion. Diagnosis of MI was made using the American College of Cardiology and European Society of Cardiology guidelines for acute, evolving, or recent MI. ST-segment elevation and non−ST-segment elevation MI were included. These guidelines require a characteristic increase and decrease of troponin or creatine kinase-MB with ≥1 of the following: ischemic symptoms, the development of pathologic Q waves on electrocardiography, ST-segment elevation or depression, coronary intervention, or pathologic findings of an acute MI. The occurrence of stent thrombosis

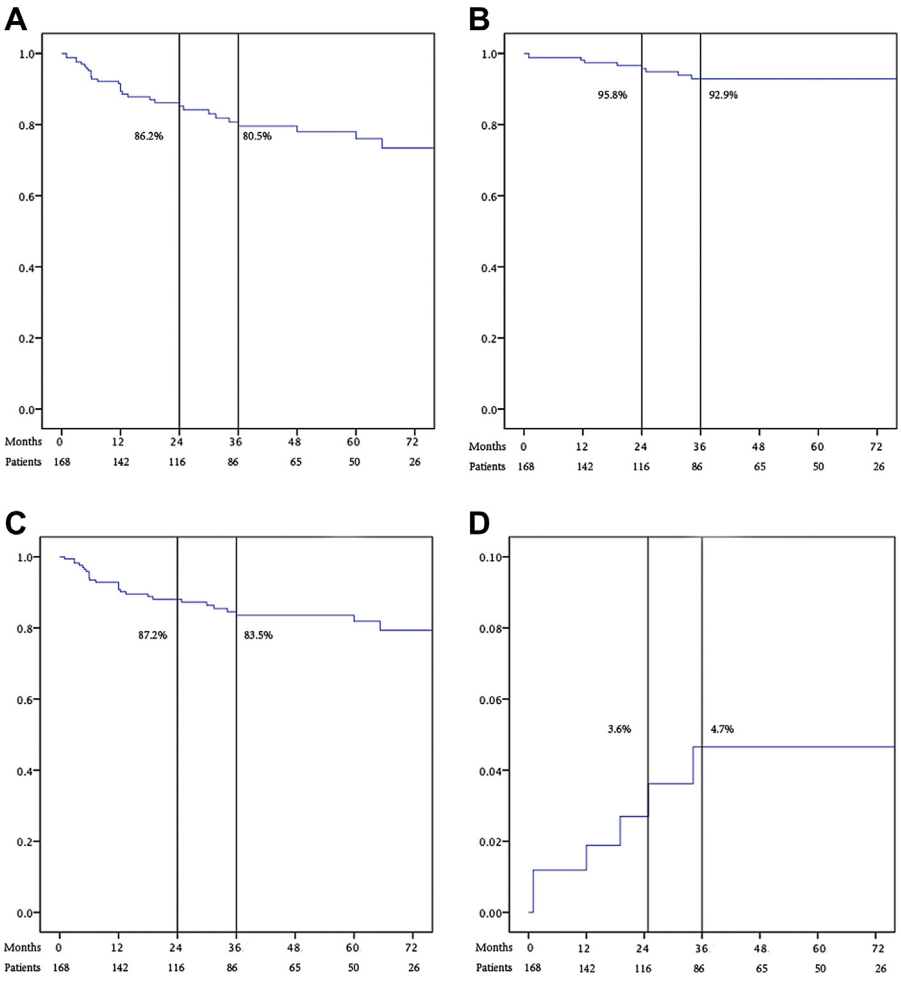

Figure 1. Kaplan-Meier survival curves of cumulative MACEs *(A)*, death or MI *(B)*, TVR-free survival *(C)*, and stent thrombosis *(D)*.

was defined on the basis of the Academic Research Consortium definition.[9] Stent thrombosis was defined as acute, subacute, late, or very late if the event occurred <24 hours, <30 days, <1 year, or >1 year after the procedure, respectively.

All continuous variables are reported as mean ± SD and categorical variables as frequencies. Cumulative event rates were evaluated using Kaplan-Meier curves. Cumulative events were calculated at 2-year and median follow-up. Univariate and multivariate analyses were performed to identify independent predictors of adverse events. Specifically, all variables significantly associated with the clinical event of interest on univariate analysis ($p < 0.10$) were entered into subsequent models. After appropriate checks for underlying assumptions, multivariate Cox proportional-hazards analyses were performed for all pertinent covariates. The results of the multivariate Cox analyses are reported as hazard ratios (HRs) with 95% confidence intervals (CIs) and p values. A 2-tailed p value <0.05 was considered statistically significant. All analyses were performed using SPSS for Windows version 18.0.1 (SPSS, Inc., Chicago, Illinois).

Results

The baseline characteristics of participants are listed in Table 1. From February 2003 to December 2011, 168 patients (average age 40.3 ± 2.0 years) underwent PCI and stent implantation. One hundred fifty-seven of the patients (93.5%) had ≥1 of the conventional risk factors (hypertension 51.6%, hyperlipidemia 72%, smoking 4.8%, overweight 43.9%, family history 10.8%, diabetes 31.8%). Forty patients (30%) had blood pressure >140/90 mm Hg on admission, almost half had low high-density lipoprotein cholesterol (<40 mg/dl), and 1/3 had high triglyceride (>150 mg/dl).

Autoimmune or connective tissue diseases were present in 6.5% of the population. About 4% of the population also had gynecologic diseases, 4 of whom had ovarian disease (oophoritic cysts or ovariotomy) and 2 of whom had uterine disease (endometriosis or hysterectomy). Four patients had symptoms beginning <6 months postpartum.

ST-segment elevation MI was the clinical presentation in 25.7% of the population. ST-segment elevation MI was also more frequent in patients with autoimmune or connective tissue disease (54.5%). All 9 patients who were taking contraceptives presented with acute MI (3 with non−ST-segment elevation MI, 6 with ST-segment elevation MI).

Coronary angiographic characteristics are listed in Table 2. Single-vessel disease was present in 2/3 of patients, often involving the left anterior descending coronary artery

Table 4
Multivariate analysis showing independent predictors of major adverse cardiac events

Variable	Significance	Exp(B)	95% CI for Exp(B)
Anterior MI	0.04	2.73	1.06−7.03
Age	0.62	1.03	0.92−1.15
Triple-vessel disease	0.31	1.76	0.59−5.29
Immunology	0.007	3.60	1.43−9.08
Ejection fraction <50%	0.02	3.97	1.19−13.19
Smoking	0.04	4.89	1.09−23.06
Hypertension	0.01	3.07	1.30−7.24
Diabetes	0.21	0.52	0.19−1.43
Hyperlipidemia	0.70	0.84	0.3−2.01
Obesity	0.48	1.25	0.68−2.31
Family history	0.39	1.31	0.70−2.46
Bare-metal stent	0.65	0.71	0.16−3.16

Table 5
Cumulative events at 2 years compared with a pool analysis of 3 trials taking all comers[11] and a retrospective trial including young patients with stent implantation[5]

	Male Patients[11]	Female Patients[11]	Young Patients (88.3% Men)[5]	Young Women (This Study)
Age	63.1 ± 10.1	67.1 ± 10.5	36.3 ± 3.5	40.3 ± 2.0
Number of patients	3,721	1,164	224	168
DES	100%	100%	43.3%	95%
MACEs			10.4%	13.8%
Death or MI	6.6%	8.2%	3.2%	4.2%
TVR	7.5%	6.4%	6.5%	12.7%
Stent thrombosis	2.2%	2.2%	1.8%	3.6%

(84.3%). A total of 12 bare-metal stents and 256 DES (95.6%) were implanted. Spontaneous dissection was noted in 3 patients, 2 of whom were postpartum. Of these, 2 patients were diagnosed by coronary angiography and 1 by intravascular ultrasound and optical coherence tomography.

The incidence of in-hospital, short-term (30 days and 1 year), and long-term (median 3 years) adverse events is reported in Table 3. During the hospital stay, there was 1 death secondary to acute thrombosis after left main coronary artery DES implantation in a patient with Takayasu's arteritis. One acute MI occurred secondary to acute thrombosis in a patient who took contraceptives. The incidence of in-hospital MACEs was 1.2%.

At 30-day follow-up, no additional adverse events had occurred. After a median follow-up period of 36 months (interquartile range 15 to 60), 3 patients had died. Two patients died within 1 year, 1 from heart failure and the other during CABG for revascularization of an in-stent stenosis. The last patient died 2 years after index PCI. Overall mortality was 2.4%, and the incidence of MI was 4.2%.

Coronary angiographic follow-up was performed in 60% of patients, of whom 59 were readmitted for ischemic events. In-stent restenosis was found in 30 patients (28 with DES, 2 with bare-metal stents), and 28 underwent TVR (21 repeat PCI, 7 repeat CABG). Most TVR (63%) occurred within the first year after stent implantation. Three patients had new lesions and underwent revascularization. One patient had a stent fracture <1 year after sirolimus-eluting stent implantation.

Stent thrombosis occurred in 6 patients (3.5%): 2 acute, 1 late, and 3 very late. Of these patients, 3 had autoimmune disease (1 with rheumatic arteries and Sjögren's syndrome, 2 with Takayasu's arteritis).

Kaplan-Meier survival curves of cumulative MACEs, death or MI, TVR-free survival, and stent thrombosis are shown in Figure 1. Cumulative MACE-free survival at 2 and 3 years was 86.2% and 80.5%, respectively. TVR-free survival at 2 and 3 years was 87.2% and 83.5%, respectively. Cumulative rates of stent thrombosis at 2 and 3 years were 3.6% and 4.7%, respectively.

On multivariate analysis, smoking (HR 4.89, 95% CI 1.09 to 23.06, $p = 0.04$), hypertension (HR 3.07, 95% CI 1.30 to 7.24, $p = 0.01$), immunologic disease (HR 3.60, 95% CI 1.43 to 9.08, $p = 0.0007$), anterior MI (HR 2.73, 95% CI 1.06 to 7.03, $p = 0.04$), and a left ventricular ejection fraction <50% (HR 3.97, 95% CI 1.19 to 13.19, $p = 0.02$) were independent predictors of MACEs (Table 4).

Discussion

Historically, women have experienced more complications and early mortality after revascularization.[10] More recent studies have suggested that this gender gap is narrowing.[9] A recent registry showed that younger women hospitalized with acute MIs had a poorer prognosis than men.[11] However, there was no evidence of outcomes in younger women who underwent PCI. The results of our study show that for a median 3-year follow-up period, the overall mortality rate after PCI was 2.4% and the TVR rate was 16.7%.

We compared the outcomes of our study with a recent pool analysis of 3 randomized DES trials taking all comers (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization [SIRTAX], Limus Eluted From a Durable Versus Erodable Stent Coating [LEADERS], and RESOLUTE)[12] and 1 recent retrospective research that included a predominantly young male CAD population who underwent stent implantation (see Table 5). We found that PCI in our group of young women had worse outcomes at 2-year follow-up, driven by an increased rate of TVR. The results indicates that although conventional risk factors remain a dominant issue, some nonconventional risk factors, such as autoimmune diseases, may contribute to the worse long-term outcomes.

Premenopausal women were protected from CAD. However, epidemiologic data suggested that 13% of United States women aged 30 to 34 years already displayed advanced coronary artery lesions susceptible to rupture.[13] In our study group, the traditional coronary risk factors commonly existed. Hypertension was proved to be a predicative risk factor for adverse long-term outcomes. This indicated the importance of controlling blood pressure not only for preventing coronary disease but also to avoid the risk for clinical events after PCI. In this study, 70% of the patients had ≥1 lipid abnormality. Low high-density lipoprotein cholesterol and high triglyceride are most common types of hyperlipidemia in young women with CAD. This coincides with previous findings in elderly women.[14] Smoking was not a common risk factor for young women, as reported in young men. However, similar

to other population, smoking is predictive of worse outcomes. Pathologic studies of the coronary arteries in patients with sudden death showed that plaque erosion was the most common type of unstable plaque in premenopausal young women. The only risk factor was smoking.[5] Thus, smoking discontinuation should be encouraged in young female smokers. Overweight and obesity were fairly common in our group but were not proved to be predicative of poor outcomes after PCI.

In this study, we also found that autoimmune disease in young women is a significant predictive factor for MACEs. Patients with autoimmune diseases are likely to have multivessel disease, more likely to present with thrombotic lesions, and more prone to restenosis after intervention. Previous studies showed that patients with systemic lupus erythematosus and antiphospholipid syndrome who underwent PCI had poor outcomes.[15–17] The potential causes for increased restenosis rates and accelerated atherosclerosis in patients with autoimmune disease are numerous, probably because of induced endothelial dysfunction as well as enhanced platelet aggregation and low-density lipoprotein oxidization.[15,18] Most of our patients did not undergo autoimmune disease screening. The real number of patients with autoimmune diseases may have been underestimated.

Estrogen has beneficial effects in protecting premenopausal women from CAD. One study showed that a decreased concentration of estrogen might be an additional pathogenetic factor for the development of coronary heart disease in menstrually active premenopausal women.[19] In this study, we included patients with ovarian cysts and those who had undergone oophorectomy. We noticed that patients taking contraceptives had a remarkable percentage of thrombotic lesions.

CAD in young women aged <45 years may have an origin other than atheroma, such as spontaneous coronary dissection.[20] At our center, spontaneous dissection or intramural hematoma was not a focus of attention until only recently, when intravascular ultrasound and optical coherent tomography became available. Misdiagnosis and overtreatment with stenting may have existed in our group. Thus, intravascular ultrasound and optical coherent tomography should be a focus of future research in young women with CAD without overt CAD risk factors.[21]

In this study, we identified that the left anterior descending coronary artery was the most affected artery and that anterior MI was among the significant predictors of worse clinical outcomes. This could partially explain why young female patients had increased mortality after acute MI in comparison with older female and male patients. One study showed that direct angioplasty eliminates gender differences in mortality early after acute MI.[22] Our study showed that PCI in young women had a low mortality rate, but revascularization in the target vessel tended to be more frequent.

Disclosures

The authors have no conflicts of interest to disclose.

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