Short- and Long-term Outcomes in Patients with Connective Tissue Diseases Undergoing Percutaneous Coronary Intervention

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Abstract

Background: Coronary artery disease (CAD) is a leading cause of morbidity and mortality in patients with connective tissue diseases (CTDs). Risk factors and clinical characteristics in these patients are not equivalent to those in traditional CAD patients. The objective of this study was to report short- and long-term clinical outcomes in a consecutive series of patients with CTD who underwent percutaneous coronary intervention (PCI) with stent implantation.

Methods: The study group comprised 106 consecutive patients with CTD who underwent PCI in Beijing Friendship Hospital between January 2009 and June 2012. Medical records were analyzed retrospectively including clinical basic material, coronary angiogram data, and the incidence of major adverse cardiac events (MACEs) during the short- and long-term (median 3 years) follow-up.

Results: Ninety-two of the patients (86.8%) had one or more traditional CAD risk factors. Multivessel disease was present in more than 2/3 of patients (73.6%). The left anterior descending coronary artery was the most commonly affected vessel (65.1%). Five bare-metal stents and 202 drug-eluting stents were implanted. After a median follow-up period of 36 months, thirteen patients (12.3%) died from cardiac causes, the rate of stent thrombosis was 9.4%, and the rate of target vessel revascularization (TVR) was 14.2%. Multivariate analysis revealed that hypertension (hazard ratio [HR] = 3.07, 95% confidence interval [CI]: 1.30–7.24, P = 0.041), anterior myocardial infarction (HR = 2.77, 95% CI: 1.06–7.03, P = 0.04), longer duration of steroid treatment (HR = 3.60, 95% CI: 1.43–9.08, P = 0.032), and C-reactive protein level >10 mg/L (HR = 3.98, 95% CI: 1.19–12.56, P = 0.036) were independent predictors of MACEs.

Conclusions: Patients with CTD and CAD may have severe coronary lesions. PCI in these patients tends to result in an increased rate of stent thrombosis and TVR during long-term follow-up, which may be influenced by traditional and nontraditional risk factors.

Key words: Connective Tissue Disease; Coronary Artery Disease; Percutaneous Coronary Intervention

INTRODUCTION

Connective tissue diseases (CTDs) are autoimmune systemic diseases those affect multiple organs including the heart. Premature atherosclerosis and cardiovascular disease risks are enhanced in patients with certain CTDs such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic vasculitis, and antiphospholipid syndrome.[1-4] Coronary artery disease (CAD) due to premature atherosclerosis is a leading cause of morbidity and mortality in this population.[5] The risk factors and clinical characteristics in this subset of patients are not equivalent to those of patients with traditional CAD.[6,7] The therapeutic approach can be challenging, and the best interventional treatment for CAD in these patients remains undetermined.[8] Some studies have examined outcomes after percutaneous coronary intervention (PCI), but they have produced conflicting results. A study found that outcomes were similar in patients with RA and well-matched non-RA patients undergoing PCI.[9] In contrast, a recent study showed that RA and SLE were associated independently with overall mortality during long-term follow-up in patients who had

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undergone PCI.[10] Thus, the objective of this study was to report the short- and long-term clinical outcomes in a consecutive series of patients with CTD who underwent PCI with stent implantation.

METHODS

Patients

One hundred and six consecutive patients with CTD who underwent PCI and stent implantation for CAD between 2009 and 2012 were retrospectively analyzed. These patients were included from cardiac catheterization registry with a yearly volume of 1200–1500 PCIs of Beijing Friendship Hospital (China). According to the latest criteria of the American College of Rheumatology, rheumatology specialists made all CTD diagnoses before admission. Coronary lesions were considered to be significant with >70% stenosis in a major epicardial coronary artery.

On admission, patients underwent thorough clinical examination, and complete histories were taken, with special attention to the previous history of myocardial infarction (MI), period of steroid treatment, and CTD history. The following data were recorded: age, gender, body mass index (BMI), cholesterol, triglyceride, serum creatinine, fasting blood glucose levels, white blood cell, platelet counts, inflammatory markers (C-reactive protein [CRP] level and erythrocyte sedimentation rate), presence of autoantibodies, and left ventricular ejection fraction.

No patient was excluded from the analysis. Informed consent was obtained from each patient. The study was in agreement with the guidelines approved by the Institutional Ethics Committee of Beijing Friendship Hospital. All available inpatient and outpatient medical records were reviewed. Information regarding patients' clinical status at the latest clinical follow-up available was collected by clinical visits and telephone interviews.

Definitions of risk factors

Traditional risk factors included obesity, smoking, hypertension, hyperlipidemia, diabetes mellitus, and family history of early CAD. Patients with BMI >28 kg/m^2 were considered to be obese. Smoking was defined as regularly smoking one or more cigarette daily or smoking cessation within the past 12 months. Patients who had stopped smoking >2 years before the onset of disease were classified as nonsmokers. Hypertension was diagnosed when the average of three or more blood pressure measurements obtained during hospitalization exceeded 140/90 mmHg, or if a previous diagnosis of hypertension had been made. Hyperlipidemia was defined as total cholesterol >5.18 mmol/L, low-density lipoprotein cholesterol >3.37 mmol/L, high-density lipoprotein cholesterol <1.04 mmol/L, or triglyceride >1.7 mmol/L.[11] Fasting blood glucose levels were obtained within the first 48 h of hospitalization. Diabetes mellitus was diagnosed by a fasting blood glucose level >7.0 mmol/L, a random plasma glucose level >11.1 mmol/L, or a history of diabetes mellitus

including those treated with diet control, oral medications, or insulin.[12] The family history of early CAD was defined as any direct blood relatives (parents, siblings, and children) who have had any of the following at <55 years of age in a male and <65 years of age in a female: angina, MI, or sudden death without obvious cause.

Coronary procedures and adjunctive antiplatelet therapy

PCI and intracoronary stent implantation were performed according to current guidelines and using standard percutaneous techniques. Choosing the type of stent was at the discretion of the operator and each operator relied on his own judgment to assess stent expansion. All patients were on aspirin and received a 5000–10,000 unit boluses of unfractionated heparin before the procedure. Patients also received 300–600 mg oral clopidogrel initiated either before or in the catheterization laboratory at the discretion of the operator, and continued at the dose of 75 mg/d for at least 1 month in bare-metal stents (BMSs) and 12 months in drug-eluting stents (DESs). Platelet glycoprotein IIb/IIIa antagonists were used on the discretion of the operator.

Outcome measure

The study end point was the incidence of major adverse cardiac events (MACEs) including cardiac death, MI, target vessel revascularization (TVR; repeat PCI or coronary artery bypass grafting [CABG]) and stent thrombosis at immediate (in-hospital), short-term (30 days and 1 year), and long-term (median 3 years) follow-up. Cardiac death was defined as death caused by MI, or heart failure and sudden death. Stent thrombosis was defined as symptoms suggestive of an acute coronary syndrome and angiographic confirmation of stent thrombosis. Clinical outcome data were collected until June 30, 2015.

Statistical analysis

The SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA) software package was employed for statistical processing. All continuous variables are reported as a mean ± standard deviation (SD) and categorical variables are reported as frequencies. Cumulative event rates were evaluated using Kaplan–Meier curves. Univariate and multivariate analyses were performed to identify independent predictors of adverse events. Specifically, all variables significantly associated ($P < 0.10$) with the clinical event of interest on univariate analysis were entered into subsequent models. After appropriate testing of underlying assumptions, multivariate Cox proportional–hazards analyses were performed for all pertinent covariates. The results of the analyses are reported as hazard ratios (HRs) with 95% confidence intervals (CIs) and P values. Two-tailed $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics

The baseline characteristics of participants are shown in Table 1. From January 2009 to December 2012,

106 patients (average age 60.2 ± 10.1 years) underwent PCI and stent implantation. Fifty-four patients had RA, 38 had Sjögren's syndrome, 11 had SLE, and three patients had Behcet's disease. The mean duration of follow-up was 36 (interquartile range: 32–44) months after hospital discharge. Ninety-two of the patients (86.8%) had one or more of the traditional risk factors (hypertension, 83.0%; hyperlipidemia, 57.5%; diabetes, 41.5%; smoking, 17.9%; obese, 14.2%; and family history of early CAD, 11.3%). Almost one-fifth (21.7%) of patients had received steroid treatment for more than 1 year. Rheumatoid factor or autoantibody positivity was detected in 42.5% of patients. Thrombocytopenia (platelet count <150 × 10^9/L) were present in 5.7% of the population.

ST-segment elevation MI was the clinical presentation in 31.1% of patients, 20 of whom had anterior MI and 13 of whom had inferior MI. All three patients with Behcet's disease presented with acute MI.

Coronary angiographic characteristics
Coronary angiographic characteristics are listed in Table 2. Multivessel disease was present in 73.6% of patients. The left anterior descending coronary artery was involved in 69 (65.1%) patients. Eleven (10.4%) patients were diagnosed as chronic total occlusion by coronary angiography. Coronary artery ectasia was noted in six patients. A total of five BMSs and 202 DESs were implanted. Complete revascularization was performed in 32 (30.2%) patients. Long (>20 mm) stents were implanted in 91 (85.8%) patients.

Clinical outcomes
The incidence of MACEs during hospitalization, short-term (30 days and 1 year), and long-term (median 3 years) follow-up is reported in Table 3. In-hospital period, the incidence of adverse events was 4.7%. At 30 days postdischarge, two additional acute MIs had occurred. During the long-term follow-up period, 13 (12.3%) patients died from cardiac causes, including MI (six patients), heart failure (four patients), and sudden death (three patients); three patients died from infection or renal insufficiency. Ten (9.4%) acute MIs occurred secondary to stent thrombosis, eight of them occurred <1 year after stent implantation. Four of these patients had SLE, three had RA, one had Sjögren's syndrome, and two had Behcet's disease. Fifteen patients underwent TVR (12 repeat PCI, three repeat CABG), in nine cases, TVR was performed within the 1st year after the procedure. Seven of these patients had new lesions and underwent revascularization.

A Kaplan–Meier survival curve of cumulative MACEs is shown in Figure 1. Cumulative MACE-free survival at 3 years was 77.5%, respectively. On multivariate analysis, hypertension ($HR = 3.07, 95\% CI$: 1.30–7.24, $P = 0.041$), steroid treatment for more than 1 year ($HR = 3.60, 95\% CI$: 1.43–9.08, $P = 0.032$), anterior MI ($HR = 2.77, 95\% CI$: 1.06–7.03, $P = 0.04$), and CRP > 10 mg/L ($HR = 3.98, 95\% CI$: 1.19–12.56, $P = 0.036$) were independent predictors of MACEs [Table 4].

Table 1: Baseline clinical characteristics of patients with CTD who underwent PCI with stent implantation (*n* = 106)

Characteristics	Values
Age (years)	60.2 ± 10.1
Sex (male), *n* (%)	17 (16.0)
Hypertension, *n* (%)	88 (83.0)
Diabetes, *n* (%)	44 (41.5)
Family history of early CAD, *n* (%)	12 (11.3)
Hyperlipidemia, *n* (%)	61 (57.5)
Smoking, *n* (%)	19 (17.9)
Obesity (BMI >28 kg/m^2), *n* (%)	15 (14.2)
Previous history of myocardial infarction, *n* (%)	6 (5.7)
LVEF <50%, *n* (%)	17 (16.0)
>1-year steroid treatment, *n* (%)	23 (21.7)
CTD duration >10 years, *n* (%)	34 (32.7)
Serum creatinine level (μmol/L)	86.2 ± 16.8
White blood cell count >10×10^9/L, *n* (%)	20 (18.9)
Platelet count <150×10^9/L, *n* (%)	6 (5.7)
Erythrocyte sedimentation rate (mm/h)	33.2 ± 18.3
C-reactive protein level >10 mg/L, *n* (%)	39 (36.8)
Rheumatoid factor positivity, *n* (%)	36 (34.0)
Autoantibody positivity, *n* (%)	42 (39.6)
CTD, *n* (%)	
Rheumatoid arthritis	54 (50.9)
Systemic lupus erythematosus	11 (10.4)
Sjögren's syndrome	38 (35.9)
Behcet's disease	3 (2.8)
CAD, *n* (%)	
NSTEMI	18 (17.0)
Anterior myocardial infarction	20 (18.9)
Inferior myocardial infarction	13 (12.2)
Unstable angina pectoris	55 (51.9)

Data were expressed as a mean ± SD or *n* (%). CTD: Connective tissue disease; PCI: Percutaneous coronary intervention; BMI: Body mass index; LVEF: Left ventricular ejection fraction; NSTEMI: Non-ST-segment elevated myocardial infarction; CAD: Coronary artery disease; SD: Standard deviation.
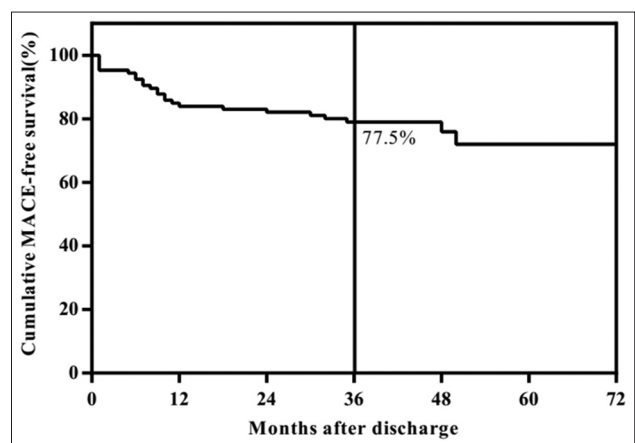

Figure 1: The Kaplan–Meier survival curve of cumulative major adverse cardiac events (MACE).

Discussion

Previous studies have suggested that patients with CTD have high morbidity due to MI and high cardiovascular mortality.[5]

Table 2: Coronary angiographic and clinical characteristics of patients with CTD who underwent PCI with stent implantation (*n* = 106)

Characteristics	Values
Single-vessel disease, *n* (%)	16 (15.1)
Multivessel disease, *n* (%)	78 (73.6)
Chronic total occlusion, *n* (%)	11 (10.4)
Coronary artery ectasia, *n* (%)	6 (5.7)
Stented coronary artery, *n* (%)	
Left main	15 (14.2)
Left anterior descending	69 (65.1)
Left circumflex	32 (30.2)
Right	46 (43.4)
Average stent length per vessel (mm)	28.1 ± 13.2
Average number of stents per vessel	1.7 ± 1.0
Stent length >20 mm, *n* (%)	91 (85.8)
Bifurcation stent, *n* (%)	12 (11.3)
Complete revascularization, *n* (%)	32 (30.2)
Stent type, *n* (%)	
Drug-eluting	202 (97.6)
Bare-metal	5 (2.4)

Data were expressed as a mean ± SD or *n* (%). CTD: Connective tissue disease; PCI: Percutaneous coronary intervention; SD: Standard deviation.

Table 3: Incidence of MACEs during hospital, short-term (30 days and 1 year), and long-term (median 3 years) follow-up (*n* (%))

Events	In-hospital	≤30 days postdischarge	≤1 year postdischarge	Long-term (median 3 years)
MACEs	5 (4.7)	7 (6.6)	17 (16.0)	24 (22.6)
Cardiac death	2 (1.9)	2 (1.9)	7 (6.6)	13 (12.3)
MI	4 (3.8)	6 (5.7)	13 (12.3)	18 (17.0)
TVR	2 (1.9)	2 (1.9)	9 (8.5)	15 (14.2)
Repeat PCI	2 (1.9)	2 (1.9)	8 (7.6)	12 (11.3)
Repeat CABG	0	0	1 (0.9)	3 (2.8)
Stent thrombosis	2 (1.9)	2 (1.9)	8 (7.6)	10 (9.4)
Heart failure	2 (1.9)	2 (1.9)	4 (3.8)	9 (8.5)

MACE: Major adverse cardiac events; MI: Myocardial infarction; TVR: Target vessel revascularization; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting.

However, data on these outcomes in patients with CTD who have undergone PCI are lacking. The results of our study show that the overall mortality rate after PCI in such patients was 15.1%, the stent thrombosis rate was 9.4%, and the TVR rate was 14.2% during a median follow-up period of 3 years.

We compared the outcomes of our study with a retrospective DES trials taking all comers (comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers [COMPARE]) [Table 5].[13] We found that worse outcomes in our group of patients with CTD at the 2-year follow-up time point, driven by the increased rates of MI and stent thrombosis.

Among traditional coronary risk factors, hypertension and hyperlipidemia, but not smoking or obese, were common

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

Variables	*P*	Exp(B)	95% *CI* for Exp(B)
Hypertension	0.041	3.07	1.30–7.24
Age	0.720	1.07	0.92–1.15
>1 year steroid treatment	0.032	3.60	1.43–9.08
Anterior MI	0.040	2.77	1.06–7.03
CRP >10 mg/L	0.036	3.98	1.19–12.56
Diabetes	0.950	1.76	0.59–5.29
Multivessel disease	0.410	4.89	1.09–22.06

CI: Confidence interval; MI: Myocardial infarction; CRP: C-reactive protein.

Table 5: Cumulative events at 2 years compared with the COMPARE trial

Events	EES COMPARE trial	PES COMPARE trial	This study
Age (years)	62.9	63.6	60.2 ± 10.1
Number of patients	897	903	106
MACEs (%)	9.00	13.70	17.90
Cardiac death	2.20	1.80	7.50
MI	3.90	7.50	14.20
TVR	3.00	7.60	9.40
Stent thrombosis	0.90	3.90	7.60

EES: Everolimus-eluting stent; PES: Paclitaxel-eluting stent; MACEs: Major adverse cardiac events; MI: Myocardial infarction; TVR: Target vessel revascularization.

in our study population. Although traditional risk factors remain a dominant focus, some nontraditional risk factors, such as inflammatory markers and steroid treatment, may negatively affect long-term outcomes.[14] CTDs are generally characterized by chronic inflammation and the requirement for steroid treatment. In a previous study, serum CRP level was higher in patients received steroid therapy than in those who did not, suggesting that the currently recommended steroid therapy does not control the inflammation in these patients.[15] Patients with higher serum CRP level and longer duration of steroid treatment were at increased risk of MACEs in our study group.

In this study, we also found that patients with CTD are likely to have multivessel disease. Recent studies have suggested that the clinical manifestations of CAD in SLE result from several pathophysiological mechanisms including atherosclerosis, arteritis, thrombosis, embolization, spasm, and abnormal coronary flow.[16,17] In our population, CAD may have had an origin other than an atheroma, such as coronary artery ectasia, especially in patients with SLE. Systemic inflammation may be associated with the coronary artery ectasia.[18]

The rate of stent thrombosis was high in our study population, and late stent thrombosis (31 days to 1 year postprocedure) accounted for more than half of cases. In general, stent thrombosis occurs more frequently in patients with complex lesions such as those with acute coronary syndromes, small vessels, bifurcation lesions, chronic total

occlusion, and multiple or long stents.[19] In our study, long stents were implanted in 91 (85.8%) patients. Patients with Behcet's disease have the highest rate (66.7%) of stent thrombosis, all of them presented with acute ST-segment elevation MI. However, endothelial dysfunction may also have played an important role in stent thrombosis in our study population. Endothelial dysfunction is a widespread phenomenon in patients with CTD, associated with aspects of stent thrombosis pathogenesis such as incomplete endothelialization.[20]

This study has several limitations. First, a case–control study would have been the best approach to the examination of this issue. Second, this study failed to estimate the true magnitude of the contributions of variables such as different CTD, disease activity, and therapy to the clinical outcomes of relevance. In our study, detailed quantitative data on coronary angiography were not available. Moreover, data regarding which kind of DES was implanted in the patients were not available. As a single-center, retrospective research, we cannot conclude that the CTD is associated with increased MACEs morbidity.

In conclusion, this study showed that patients with CTD and CAD may have severe coronary lesions. Stent thrombosis and TVR tended to be more frequent at long-term follow-up. In addition to the traditional CAD risk factors, longer duration of steroid treatment and high CRP level were independent predictors of adverse events. Further research on this topic is needed. Large, prospective, longitudinal studies could help to determine the true prevalence of CAD in this population and confirm risk factors.

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Conflicts of interest
There are no conflicts of interest.

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