Short-term Follow-up Results of Drug-eluting Stenting in Premature Coronary Artery Disease Patients with Multiple Atherosclerotic Risk Factors

Ming-Hsiung Wang[1,2], Wen-Lieng Lee[1,3], Kuo-Yang Wang[1,4], Yu-Cheng Hsieh[1,3], Tsun-Jui Liu[1,3], I-Hsiang Lin[1,5], Wei-Wen Lin[1], Chih-Tai Ting[1,3], Kae-Woei Liang[1,3]*

[1]Cardiovascular Center, Taichung Veterans General Hospital, Taichung, [2]Fong-Yuan Hospital, Fong-Yuan, [3]Institute of Clinical Medicine, Cardiovascular Research Center, and Department of Medicine, National Yang Ming University School of Medicine, Taipei, [4]Department of Medicine, Chung Shan Medical University, Taichung, and [5]Nantou Hospital, Nantou, Taiwan, R.O.C.

Background: Premature coronary artery disease (CAD) is a special entity with a strong link to familial hypercholesterolemia, family history of premature CAD, or multiple coexistent atherosclerotic risk factors. Drug-eluting stenting (DES), including paclitaxel-eluting stenting (PES) and sirolimus-eluting stenting (SES), has been proven to have a lower restenotic rate. However, to date, few studies have investigated the clinical and angiographic results of DES in premature CAD patients.

Methods: Between February 2004 and October 2005, premature CAD patients, defined as those younger than 50 years of age, who were treated with DES in our medical center were all retrospectively enrolled. Their baseline clinical characteristics, clinical outcome and angiographic follow-up results were analyzed.

Results: A total of 26 patients (M/F: 23/3) were enrolled, with a mean age of 44 ± 6 years (range, 24–50 years). Conventional atherosclerotic risk factors were prevalent in this study group, including diabetes mellitus (35%), hypertension (35%), hyperlipidemia (54%) and smoking (73%). Moreover, there was 1 homozygous and 1 heterozygous familial hypercholesterolemia case in our study group. In terms of angiographic results, there were 40 target lesions in 34 target vessels. Forty DES (39 PES, 1 SES) were implanted with a median stent diameter of 3 mm and median length of 24 mm. The clinical follow-up was counted up to May 2006, with a mean follow-up duration of 540 ± 168 days; 11 (42%) patients had a second angiogram during the follow-up period (200 ± 98 days after DES). None of the patients had target lesion revascularization (TLR). In addition, there was no difference in TLR or stent thrombosis between patients with or without acute coronary syndrome.

Conclusion: Based on our single-center experience, DES had good short-term follow-up results for a premature CAD group with diverse and multiple atherosclerotic risk factors. [*J Chin Med Assoc* 2008;71(7):342–346]

Key Words: acute coronary syndrome, coronary artery disease, drug-eluting stent, familial hypercholesterolemia, premature CAD

Introduction

Premature coronary artery disease (CAD) patients are a special subgroup among atherosclerotic patients. Premature presentation implies a rapidly progressive disease course. Moreover, the impact of premature myocardial infarction (MI) or CAD on the young patient and his/her family is particularly devastating. Fortunately, the incidence of MI and symptomatic CAD in young adults is low; most studies show that only about 3% of all CAD cases occur under the age of 40.[1,2]

The fact that clinically manifest CAD in the young adult is relatively uncommon implies that these patients are atypical of the general population.[3–8] Cigarette smoking has been shown to be the single factor most strongly associated with CAD in young adults.[9] Kannel et al found that in patients included in the Framingham

*Correspondence to: Dr Kae-Woei Liang, Cardiovascular Center, Taichung Veterans General Hospital, 160, Section 3, Taichung-Kang Road, Taichung 407, Taiwan, R.O.C.
E-mail: ekwliang@ms17.hinet.net • Received: July 25, 2007 • Accepted: May 22, 2008

Heart Study, the relative risk for CAD was about 3 times higher in smokers aged 35–44 compared to nonsmokers in the same age group.[9,10] Diabetes and hyperlipidemia are also important associated risk factors in premature CAD patients. Family history of CAD is another known risk factor and probably represents a combination of multiple risk factors.

Drug-eluting stenting (DES) has been shown to have a lower restenotic rate in comparison with bare-metal stenting.[11,12] Recently, several clinical trials and registries have proven the efficacy of DES in high-risk subsets such as diabetes, small vessels or long lesions.[13–15] However, few studies have investigated the efficacy and safety of DES for premature CAD patients, who are usually associated with multiple atherosclerotic risk factors. We conducted this retrospective study and investigated the short-term results of DES in premature CAD patients with diverse and multiple risk factors.

Methods

Study population

Between February 2004 and October 2005, premature CAD patients, defined as those younger than 50 years of age, who were treated with DES in Taichung Veterans General Hospital (Taichung, Taiwan) were all retrospectively enrolled. Their clinical characteristics, clinical outcome and angiographic follow-up results were analyzed. Angiographic follow-up was at the discretion of the interventional cardiologists in charge. The clinical follow-up was retrospectively counted up to May 31, 2006.

Definition of demographic data and conventional atherosclerotic risk factors

Acute coronary syndrome (ACS) included ST elevation or non-ST elevation MI with cardiac enzyme elevation or unstable angina with crescendo chest pain, and ischemic electrocardiographic changes but no cardiac enzyme elevation. Hypertension was defined as systolic blood pressure over 140 mmHg or diastolic blood pressure over 90 mmHg after multiple measurements in the sitting position at rest or patients already on antihypertensive medication. Diabetes mellitus was defined as fasting blood sugar over 126 mg/dL on 2 occasions or patients already on oral hypoglycemic agents or insulin shot. Hyperlipidemia was defined as total cholesterol over 200 mg/dL or low-density lipoprotein cholesterol (LDL-C) over 130 mg/dL or patients already on HMG-CoA reductase inhibitor treatment. Family history of premature CAD was defined as CAD history in a first-degree male relative before the age of 55 or female before the age of 65.

Percutaneous coronary intervention

Patients received 325 mg of aspirin and a 300-mg oral dose of clopidogrel before or immediately after the procedure. Dual antiplatelet agents were maintained for at least 3 months in sirolimus-eluting stenting (SES) and for 6 months in paclitaxel-eluting stenting (PES). The use of either PES or SES was dependent upon mutual agreement between the patient and the interventional cardiologist in charge. Target vessel revascularization (TVR) was considered to be driven by ischemia if the stenosis of the target vessel was at least 50% of the luminal diameter on the basis of a quantitative analysis, with either electrocardiographic changes while the patient was at rest or a functional study indicating ischemia in the distribution of the target vessel, or if there was stenosis of at least 70% in conjunction with recurrent symptoms alone. Target lesion revascularization (TLR) was defined as repeat revascularization for ischemia owing to stenosis of at least 50% of the luminal diameter anywhere within the stent or within the 5-mm borders proximal or distal to the stent. Target vessel failure was defined as death, MI, or ischemia-driven TVR. If an adverse event could not conclusively be attributed to a non-target vessel, the event was considered a target vessel failure.

Definition of angiographic parameters

The complete angiogram record was reviewed and angiographic measurements were made on a dedicated workstation with software for quantitative analysis of angiograms (QCA) (Philips Inturis Suite, R2.2). The classification of coronary lesion types was made based on the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines. Binary restenosis was defined as stenosis of at least 50% diameter of the luminal diameter of previously treated lesions.

Definition of stent thrombosis

Stent thrombosis was defined as an ACS with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel or, in the absence of angiographic confirmation, either acute MI in the distribution of the treated vessel or death from cardiac causes up to the end of the defined study period.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and categorical data as percentages.

Categorical variables were compared using the χ^2 test with or without Yate's correction as indicated. SPSS version 12.1 (SPSS Inc., Chicago, IL, USA) was used for all calculations. A 2-tailed p value less than 0.05 was considered statistically significant.

Results

Baseline demographic data and conventional atherosclerotic risk factors

A total of 26 patients (M/F: 23/3) were enrolled, with a mean age of 44 ± 6 years (median age, 45 years; range, 24–50 years). Conventional atherosclerotic risk factors were prevalent in this study group, including diabetes mellitus (35%), hypertension (35%), hyperlipidemia (54%) and smoking (73%) (Table 1). The mean number of atherosclerotic risk factors was 3 ± 2. In particular, there was 1 homozygous and 1 heterozygous familial hypercholesterolemia patient in our study. The homozygous patient was a 24-year-old woman who presented with baseline total cholesterol 520 mg/dL, tendon xanthomas, left main and triple-vessel coronary disease and carotid atherosclerosis. The heterozygous patient was a 34-year-old man with baseline total cholesterol of 400 mg/dL and triple-vessel coronary disease.

Table 1. Baseline clinical data of 26 premature coronary artery disease patients treated with drug-eluting stents*

Age (yr)	44 ± 6 (range, 24–50)
Male	23 (88)
DM	9 (35)
HT	9 (35)
Hyperlipidemia	14 (54)
Smoking	19 (73)
Family history	5 (19)
Atherosclerotic risk factor per patient	3 ± 2
Prior MI	5 (19)
Clinical diagnosis	
AMI	9 (35)
UA	7 (27)
Angina pectoris	10 (38)
LVEF (n = 19)	45 ± 13
Special condition	
Homozygous FH	1
Heterozygous FH	1

**Data presented as mean ± standard deviation or n (%). DM = diabetes mellitus; HT = hypertension; MI = myocardial infarction; AMI = acute ST elevation or non-ST elevation MI; UA = unstable angina; LVEF = left ventricular ejection fraction; FH = familial hypercholesterolemia.*

Baseline angiographic data of premature CAD patients treated with DES

There were 40 target lesions in 34 target vessels. Among the 40 lesions, 25 (62.5%) were type C lesions and 24 (60%) had reference vessel diameter < 3 mm. The mean lesion length was 23.1 ± 5.2 mm. Forty DES (39 PES, 1 SES) were implanted, with a median stent diameter of 3 mm and median length of 24 mm (Table 2).

Follow-up results of premature CAD patients treated with DES

The clinical follow-up was counted up to May 2006 with a mean follow-up duration of 540 ± 168 days.

Table 2. Baseline angiographic data of premature coronary artery disease patients treated with drug-eluting stents (DES)

Target vessel (n = 34)	
LAD	17 (50.0%)
LCX	7 (20.6%)
RCA	9 (26.4%)
LM	1 (3.0%)
Target lesion type (n = 40)	
A	1 (2.5%)
B	14 (35.0%)
C	25 (62.5%)
Reference vessel diameter (n = 40)	2.96 ± 0.34 mm
< 3.0 mm	24 (60%)
≥ 3.0 mm	16 (40%)
Lesion length (n = 40)	23.1 ± 5.2 mm
Minimal vessel diameter (n = 40)	0.3 ± 0.2 mm
Stenosis (n = 40)	91.0 ± 7.6% of luminal diameter
Median stent diameter	3 mm
Median stent length	24 mm
Stent per patient	
1	14 (54%)
2	10 (38%)
3	2 (8%)
Type of DES (PES/SES)	39/1
Final reference vessel diameter	3.1 ± 0.4 mm
Final minimal luminal diameter	3.1 ± 0.4 mm
Final stenosis	2% of diameter

LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; LM = left main coronary artery; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

Eleven (42%) patients had a second angiogram in the follow-up period (200 ± 98 days after DES) and none of them had binary restenosis (Table 3). Moreover, no patients had TLR in the clinical follow-up period. However, 2 patients (5.9% of intervened vessels) had TVR (non-target lesion) during follow-up. One was a 44-year-old man who had a patent PES site over the proximal obtuse marginal branch on follow-up angiogram but restenosis of the far-distal obtuse marginal ballooning site (beyond the stented segment). The other was a 42-year-old man, who received PES at the proximal left anterior descending artery (LAD). On follow-up, he had a patent LAD-proximal stented site, but a previously untreated LAD-middle lesion became significant and intervention was subsequently performed with balloon angioplasty. No patients developed stent thrombosis or recurrent acute MI in the clinical follow-up period. Regarding risk factor modification, the 14 patients who met the criteria for hypercholesterolemia (total cholesterol > 200 mg/dL or LDL-C > 130 mg/dL) were all put on HMG-CoA reductase inhibitor treatment during the clinical follow-up period. Forty-two percent of the original cigarette smokers quit smoking after index percutaneous coronary intervention (PCI).

Comparison of premature CAD patients with or without ACS who were treated with DES

Sixteen (62%) of the study patients were admitted due to ACS, while 10 (38%) were admitted due to stable angina pectoris. There was no difference in TLR, stent thrombosis or binary restenosis between the ACS and non-ACS groups. Two patients in the ACS group had non-target lesion TVR ($p = 0.684$ *vs.* non-ACS) (Table 4).

Table 3. Follow-up results of premature coronary artery disease patients treated with drug-eluting stents

Clinical outcome (patient number = 26; vessel number = 34; lesion number = 40)	
Mean follow-up days	540 ± 168
Death from cardiac cause (%)	0
Myocardial infarction (%)	0
Stent thrombosis (%)	0
Target lesion revascularization ($n = 40$)	0
Target vessel (non-target lesion) revascularization ($n = 34$)	2 (5.9%)
Target vessel failure ($n = 34$)	2 (5.9%)
Angiographic follow-up (patient number = 11; lesion number = 18)	
Binary restenosis	0
Follow-up duration (d)	200 ± 98

Discussion

Premature CAD demands special clinical attention because of its devastating impact on patients and their families.[16] DES is gaining popularity among cardiologists because of its effectiveness in reducing the restenosis rate.[11,12] However, concerns about the increased late or very late stent thrombosis rate in DES have recently arisen.[17,18] Though several trials and registries have proven the efficacy of DES in the general population, very few studies have focused on DES application in premature CAD groups. In our retrospective study, we showed that DES was a reliable treatment for a premature CAD group with complex lesions and diverse and multiple atherosclerotic risk factors.

Our study included 2 rare premature CAD cases with familial hypercholesterolemia. One was a homozygous 24-year-old woman who presented with baseline total cholesterol of 520 mg/dL, tendon xanthomas, left main and triple-vessel coronary disease and carotid artery stenosis. She was treated with both HMG-CoA reductase inhibitor and plasma LDL apheresis.[19] SES was implanted in the left main ostium and a PES in the right coronary artery. However, no skin biopsy was done to confirm the diagnosis by measuring LDL receptor activity in the cultured skin fibroblasts of this patient.[20] Another limitation is that there was no follow-up coronary angiogram in this case. The other patient was a heterozygous 34-year-old man with baseline total cholesterol of 400 mg/dL, ischemic resting electrocardiogram and strong positive treadmill exercise test results. Coronary angiogram showed triple-vessel coronary disease, and he was treated with a total of 5 PES in 2 PCI sessions. A radionuclide exercise myocardial perfusion scan was performed 5 months later that disclosed negative ischemic response on electrocardiography and scan, indicating good therapeutic results.

The study was based on a retrospective analysis of a single center's catheterization databank and thus limited by a small sample size. The clinical implications of

Table 4. Comparison of premature coronary artery disease patients with or without acute coronary syndrome (ACS) who were treated with drug-eluting stents

	ACS ($n = 16$)	Non-ACS ($n = 10$)	*p*
TLR	0	0	1.000
TVR	2	0	0.684
Stent thrombosis	0	0	1.000
Binary restenosis*	0	0	1.000

**Eleven patients underwent angiography during follow-up. TLR = target lesion revascularization; TVR = target vessel revascularization.*

our study are also limited by the DES brand selected (98% PES) as well as gender bias (88% male). Another limitation is that only 42% of the studied patients had a second coronary angiogram during the follow-up period. Moreover, 35% of studied patients presented with acute MI. According to the literature, young-age acute MI is associated with more thrombus and less plaque and thus an inherent lower restenotic rate.[21] Another shortcoming of this study was the lack of an older-age control group that received DES treatment in the same study time frame.

The mean number of atherosclerotic risk factors was 3 ± 2 in our study, and 63% of the treated lesions were ACC/AHA class C. Though most of the treated lesions were complex and the clinical scenarios were high risk for restenosis, our short-term follow-up results disclosed only 2 target vessel failures (5.9%). The results are compatible with most published clinical trials in high-risk subsets.[14,15] Our study results indicate that young age or premature CAD is not a limitation to DES-based PCI in current practice. Moreover, recent results from the COURAGE trial by Boden et al emphasized the importance of risk factor modification for the treatment of stable angina pectoris.[22] Our study results on young premature CAD subjects again proved this notion as all our patients with hypercholesterolemia were put on HMG-CoA reductase inhibitor treatment during the clinical follow-up period.

In conclusion, based on our single-center experience, DES was a reliable treatment with a very low TLR (0%) for a premature CAD group with complex lesions and diverse and multiple atherosclerotic risk factors.

Acknowledgments

This study was supported, in part, by grants from Yen Tjing Ling Medical Foundation (CI-95-14), and Taichung Veterans General Hospital (TCVGH-953104C), Taiwan.

References

1. Jalowiec DA, Hill JA. Myocardial infarction in the young and in women. *Cardiovasc Clin* 1989;20:197–206.
2. Klein LW, Nathan S. Coronary artery disease in young adults. *J Am Coll Cardiol* 2003;41:529–31.
3. Juan CC, Hwang B, Lee PC, Lin YJ, Chien JC, Lee HY, Meng CC. The clinical manifestations and risk factors of a delayed diagnosis of Kawasaki disease. *J Chin Med Assoc* 2007;70:374–9.
4. Fong MC, Chen KC, Leu HB, Chen LC. Coronary revascularization in a patient with immune thrombocytopenic purpura. *J Chin Med Assoc* 2006;69:436–8.
5. Lai CC, Hsiao HC, Hsiao SH, Huang WC, Chiou CW, Yeh TC, Hwang HR, et al. Role of shortened QTc dispersion in in-hospital cardiac events in patients undergoing percutaneous coronary intervention for acute coronary syndrome. *J Chin Med Assoc* 2006;69:297–303.
6. Hsiao HC, Chen CH, Kong CW, Liu CP. Acute effects of dual-chamber pacing on the left ventricular systolic function and relaxation in patients with advanced AV block and sick sinus syndrome. *J Chin Med Assoc* 2006;69:32–6.
7. Liang KW, Lee WL, Hsueh CW, Chen YT, Ting CT. Atrial demand pacemakers in sick sinus syndrome: an efficient and reliable approach in selected patients. *J Chin Med Assoc* 2003;66:709–14.
8. Wong WW, Chen TL, Yang SP, Wang FD, Cheng NC, Kuo BI, Yu KW, et al. Clinical characteristics of fatal patients with severe acute respiratory syndrome in a medical center in Taipei. *J Chin Med Assoc* 2003;66:323–7.
9. Holbrook JH, Grundy SM, Hennekens CH, Kannel WB, Strong JP. Cigarette smoking and cardiovascular diseases: statement for health professionals by a task force appointed by the Steering Committee of the American Heart Association. *Circulation* 1984;70:1114A–7A.
10. Kannel WB, D'Agostino RB, Belanger AJ. Fibrinogen, cigarette smoking, and risk of cardiovascular disease: insights from the Framingham Study. *Am Heart J* 1987;113:1006–10.
11. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315–23.
12. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221–31.
13. Morice MC, Colombo A, Meier B, Serruys P, Tamburino C, Guagliumi G, Sousa E, et al. Sirolimus- vs paclitaxel-eluting stents in *de novo* coronary artery lesions: the REALITY trial—a randomized controlled trial. *JAMA* 2006;295:895–904.
14. Dawkins KD, Grube E, Guagliumi G, Banning AP, Zmudka K, Colombo A, Thuesen L, et al. Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. *Circulation* 2005;112:3306–13.
15. Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, O'Shaughnessy CD, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA* 2005;294:1215–23.
16. Cole JH, Miller JI 3rd, Sperling LS, Weintraub WS. Long-term follow-up of coronary artery disease presenting in young adults. *J Am Coll Cardiol* 2003;41:521–8.
17. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007;356:1020–9.
18. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;356:998–1008.
19. Schuster H. High risk/high priority: familial hypercholesterolemia—a paradigm for molecular medicine. *Atherosclerosis* 2002;(Suppl 2):27–32.
20. Civeira F. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis* 2004;173:55–68.
21. van't Hof AW, de Boer MJ, Suryapranata H, Hoorntje JC, Zijlstra F. Incidence and predictors of restenosis after successful primary coronary angioplasty for acute myocardial infarction: the importance of age and procedural result. *Am Heart J* 1998;136:518–27.
22. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503–16.