Original article

Long term efficacy and safety of Chinese made sirolimus eluting stents: results, including off label usage, from two centres over three years

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Background Multiple randomized clinical trials have demonstrated that drug eluting stents can significantly reduce the rates of restenosis and subsequent adverse events across lesion and patient. We investigated the medium term clinical efficacy and safety of Firebird sirolimus eluting stent (SES) in coronary artery disease.

Methods The sample was 509 consecutive patients with coronary artery disease (CAD) who were treated by Firebird SES and finished three-year clinical follow-up. The occurrences of major adverse cardiac events (MACE) and Academic Research Consortium defined stent thrombosis (ST) were evaluated in patients with and without diabetes mellitus.

Results Three hundred and thirty three patients (65. 4%) were treated by Firebird SES by off label indications. Angiographic success was achieved in 98.3% of the lesions. MACE and target vessel revascularization rates at 6-month, 1 year’s and 3 years’ clinical follow-up were 2.4% and 1.4%, 4.1% and 2.6%, 7.9% and 5.1%, respectively. The cumulative 3-year MACE free survival rate was 92.1%. After 3 years, DM patients had significantly higher rates of MACE (13.7% vs 6.4%, \( P < 0.05 \)) and TVR (9.8% vs 4.0%, \( P < 0.05 \)) and the cumulative MACE free survival rate was very significantly lower in the DM group (86.4% vs 93.6%, \( P < 0.05 \)). ST occurred in 7 patients (1. 4%) at the end of 3 years’ follow-up, 5 of them had definite ST with 4 cases presenting with myocardial reinfarction and 1 with unstable angina, the other 2 with probable ST had reinfarction in the stented coronary territory without angiographic follow-up. There was no difference in occurrence of ST between off label (1.5%) and on label groups (1.1%, \( P=0.07 \)).

Conclusions In daily practice, about 2/3 of patients were treated by Firebird SES by off label indications. Medium term clinical follow-up of 3 years indicated CAD patients treated by Firebird SES had a low MACE and acceptable ST rate. DM patients had higher rates of adverse events and than non DM.

Long term clinical outcomes from randomized clinical trials have shown the persisting benefit of drug eluting stent (DES) in inhibiting neointimal hyperplasia and subsequent restenosis, as compared to the bare metal stent (BMS).1-4 Inevitably, randomized trials have strict enrolment criteria, but DES is often used in other situations: so called “off label” indications.5 In China, different kinds of DES have been used in clinics for the last five years and short term clinical outcomes have been reported focusing on the Chinese made DES.6-7 The long term clinical efficacy and safety of the domestic DES are still under investigation. Here we report the three-year clinical outcomes of patients who received the Firebird sirolimus eluting stent (SES, Microport, Shanghai, China) by analyzing the data from two large percutaneous coronary intervention (PCI) centres in China.

METHODS

Sample From January 2003 to March 2005, 509 consecutive patients, who were diagnosed with coronary artery disease (CAD) and received Firebird sirolimus eluting stents (333 cases with off label indication) in Shanghai Ruijin or Beijing Fuwai hospitals provided data for this retrospective analysis. Patients who were implanted with other kinds of stent at the index procedure or whose available follow-up duration was less than three years were excluded.

PCI procedure All PCI procedures were performed following the current standard procedural guidelines as previously described.8 Aspirin (100 mg/d) and ticlopidine (250 mg, twice a day) or clopidogrel (75 mg/d) were given to all patients at least two days before PCI. Patients receiving primary PCI with stent implantation for acute myocardial infarction, had aspirin and clopidogrel with doses of 300 mg
administered before the procedure. Results of coronary angiography and PCI procedures were assessed by at least two experienced interventional cardiologists. Unfractionated heparin was given intravenously to maintain the activated clotting time >250 seconds during the procedure. Stenting success was defined as residual stenosis <20% by visual estimation and in the presence of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow in the target vessel. After procedure, all patients were advised to maintain lifelong aspirin and clopidogrel (75 mg/d) for at least 12 months.

Study endpoint and definitions
The primary endpoint was a major adverse cardiac event (MACE), defined as any death, nonfatal myocardial infarction (MI) or target vessel revascularization (TVR). MI was diagnosed by an increase in creatine kinase MB fraction of 3 times the upper limit of normal; Q wave or non Q wave MI was defined as the presence or absence of new pathological Q wave in the ECG. Occurrence of stent thrombosis (ST) was classified as definite, probable or possible according to the Academic Research Consortium recommendation. The timing of ST was categorized early (<30 days after stent implantation), late (30 days to 1 year) or very late (>1 year). Off label indications of stent implantation included: small and long lesions; chronic total occlusion; bifurcation lesion; left main disease; instent restenosis; multivessel disease; lesions in saphenous vein grafts and acute myocardial infarction.

Follow-up
All patients received telephone contact or outpatient department interview after discharge. Follow-up data for all patients were obtained from hospital records. For the patients lost during the follow-up or those with follow-up duration longer than 3 years, the survival status at last contact or 3 year was chosen as the final follow-up status.

Statistical analysis
Categorical variables were expressed as percentages and continuous variables as mean ± standard deviation. The cumulative incidence of adverse events was estimated according to the Kaplan Meier method and curves were compared using the log rank test in the subgroup analysis. A P value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (Version 10.0, SPSS Chicago).

RESULTS

Baseline and PCI characteristics
The mean age of patients was 61.8±11.1 years, 73.5% were male, 20.2% were diabetic and the mean left ventricular ejection fraction of the patients was (60.7±8.8)% (Table 1). Six hundred and forty-seven lesions were treated of which 333 patients (65.4%) were stented in off label indications. The lesion distribution and lesion type are listed in Figures 1 and 2. The mean reference vessel diameter and diameter of stenosis before implantation were (3.0±0.4) mm and (88±9)%, respectively. Direct stent implantation was performed in 27.8% of the lesions, stent to lesion length ratio was 1.35±0.12 and the number of stent per patient was 1.7±0.9. The final angiographic success rate was 98.3% of the treated lesions.

Clinical outcomes
The follow-up rates were 100.0%, 99.8%, 99.6% and 99.4% at the time of in hospital, 6 months, 1 year and 3 years, respectively. The cumulative 3 years’ MACE free survival rate was 92.1%. The details of survival status were listed in Table 2.

Diabetic compared with nondiabetic patients
The prognosis of diabetic patients (n=103, 20.2%) was poorer than non-diabetics (n=406, 79.8%, Table 3). At
Table 3. Clinical outcomes between diabetic and non diabetic patients (n (%))

<table>
<thead>
<tr>
<th>Events</th>
<th>In-hospital (n=509)</th>
<th>6-month (n=508)</th>
<th>1-year (n=507)</th>
<th>3-year (n=506)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>0 (0.2)</td>
<td>2 (0.4)</td>
<td>2 (0.4)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Q wave</td>
<td>4 (0.8)</td>
<td>4 (0.8)</td>
<td>5 (1.0)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>TVR</td>
<td>1 (0.2)</td>
<td>6 (1.2)</td>
<td>13 (2.6)</td>
<td>22 (4.3)</td>
</tr>
<tr>
<td>PCI</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>CABG</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non Cardiac</td>
<td>5 (1.0)</td>
<td>12 (2.4)</td>
<td>21 (4.1)</td>
<td>40 (7.9)</td>
</tr>
</tbody>
</table>

3 years’ follow-up, death and nonfatal MI were not significantly higher in the diabetic group, but the TVR and MACE rates were 9.8% and 4.0%, 13.7% and 6.4%, respectively, (both \( P < 0.05 \)). The cumulative MACE free survival rate was significantly lower in the diabetic group (Figure 3).

Figure 3. Three years’ MACE free survival rate between diabetic and non diabetic group.

**Dual antiplatelet therapy and stent thrombosis**

Aspirin was administered to all patients after the procedure and the mean duration of using clopidogrel after procedure was 12.2±3.4 months. Stent thrombosis occurred in 7 cases (1.4%) by 3-year follow-up; 5 were angiographically identified definite ST (one case of acute, one of late and three very late) with 4 cases of recurrent MI and 1 of unstable angina. Two patients with probable ST had recurrence of MI in the stented coronary without angiographic follow-up. The relationship between antiplatelet therapy and ST is listed in Figure 4. There was no statistical significance between the off label and on label groups regarding the occurrence of ST (1.5% and 1.1%, \( P = 0.07 \)).

Figure 4. Dual antiplatelet therapy and stent thrombosis.

**Angiographic follow-up**

One hundred and sixty-seven patients with 223 stented lesions received angiographic follow-up at a mean duration of 10.3±4.9 months. The angiographically instent and in segment restenosis rates were 5.3% and 6.4%, respectively. Most of the restenosis types were type I (40%) and type II (40%), the remaining were type IV (20%).

**DISCUSSION**

In this report, we described the medium term clinical outcomes following the use of Chinese made Firebird SES in all patients. The results demonstrated that the Firebird SES has high procedural success rate (98.4%) as a treatment for patients with CAD in daily practice, although about two thirds of the patients were treated in off label indications. The results of 3-year clinical follow-up indicated that the Firebird SES were effective and safe, with cumulative rates for death of 1.6%, Re-MI of 3.0%, TVR of 5.1% and MACE of 7.9%. The cumulative Academic Research Consortium definite or probable stent thrombosis rate was 1.4% at 3 years’ follow-up: grouped as acute ST of 0.2%, late ST of 0.4% and very late ST of 0.8%.

There is clear evidence of high efficacy of DES in reducing restenosis rate and subsequent TVR compared with BMS in randomized clinical trials of highly selected patients with de novo lesions of moderate length and diameter stenosis: listed as label indications by the manufactures.\(^1\),\(^4\),\(^11\),\(^12\) The data regarding the long term efficacy of DES in treating CAD other patients was limited. Recently, results from a pooled analysis, by Stone et al,\(^13\) which included patients implanted with Ravel, Sirius, E Sirius or C Sirius stents, indicated that 4 years’ rate of target lesion revascularisation (TLR) was...
significantly reduced in the SES group as compared with the BMS group (7.8% and 23.6, \( P < 0.001 \)), with no differences in the comparisons of stent thrombosis (1.2% and 0.6%, \( P=0.20 \)), death (6.7% and 5.3%, \( P=0.23 \)) and MI (6.4% and 6.2%, \( P=0.86 \)).

Three years’ follow-up results of RESEARCH study have shown that the Cypher SES was effective in reducing MACE (18.9%) and TLR (7.5%) compared to the BMS group (24.7% and 12.6%, respectively), which beneficial effects persisted after 2 years’ follow-up and there was no evidence of clinical late “catch up” phenomena in restenosis. The results of our study indicated that the Firebird SES had relatively lower rates of cumulative MACE (7.9%), TVR (5.1%), MI (3.0%) and death (1.6%), when compared with Cypher SES, despite the clinical scenarios of patients treated in off label indications may be more complex than those in RAVEL, SIRIUS or even the RESEARCH study. Different dosages of sirolimus loaded on the stent may lead to different degrees in inhibiting neointimal hyperplasia and subsequent MACE and TLR events. For each Firebird SES, 9 \( \mu \)g of sirolimus was loaded on per millimetre stent length, while the Cypher SES was loaded with 140 \( \mu \)g of sirolimus per square centimetre. In addition, relatively lower angiographic follow-up rate may underestimate the rate of TVR.

Patients with diabetes mellitus (DM) usually present with accelerated atherosclerosis, more diffuse disease, concomitant comorbidities and have increased risks for restenosis. For these patients, studies have shown that DES significantly reduced the restenosis compared with BMS. DIABETES trial showed that after 9 months, TLR and MACE in the SES treated group were 7.3% and 11.3%, respectively. In another recent study of diabetic patients, the DESSERT study, after 12 months the rate of MACE was 22.1%, TLR 5.9% and TVF of 14.7%. Two years’ clinical follow-up from a multicentre registry showed a TLR rate of 11.6% in the DES group. The current study showed that three years’ TVR rate was 9.8% in the DM group, which was significantly higher than the non DM patients (4.0%, \( P<0.05 \)). In addition, MACE at 3-year follow-up was significantly higher in the DM group (13.7% and 6.4%, \( P<0.05 \)), which was mainly due to the higher rate of TVR in the DM group. Current results supported the idea that DM patients have higher rates of MACE and TVR following implantation of a DES.

ST remains the major concern following DES implantation; especially the occurrence of late and very late ST. There were several recent reports addressing the safety of DES, with particular regard to ST. No significant difference was found in the rates of mortality or ST between SES and BMS at 4 years’ clinical follow-up in two analyses of major randomized SES trials. The rate of definite ST varied from 1.2% to 2.3% for Cypher SES in different studies. Daemen et al reported that the overall incidence of ST occurred in 2.9% of patients receiving DES (including sirolimus or paclitaxel eluting stent) after 3 years, with an ongoing incidence of late ST of 0.6% per year. In the current analysis, we found that the overall rate of ST (definite 1.0% and probable 0.4%) was 1.4% after 3 years in patients receiving Firebird SES, which was similar to that observed in randomized trials or meta analyses. However, the occurrence of ST in patients receiving the stent with off label indications was higher (1.5% and 1.1%, \( P=0.07 \)). It still remains unclear whether prolonged dual antiplatelet therapy would prevent or decrease the incidence of ST, especially late ST.

In our study, three patients with sub-acute definite or probable ST were on dual antiplatelet therapy at the time of the event.

The current study was a retrospective analysis with data derived from two high volume centres, but low angiographic follow-up may underestimate the rate of TVR and subsequent MACE. Only patients who received Firebird SES were included and with no control group, we could not perform comparative analyses. Multivariate analysis over subgroups, especially for predictors of ST, could not be performed with sufficient statistical power due to the small number of patients with the event.

In conclusion, by analyzing data of all patients who received Firebird SES in two large PCI volume centres, we could assess the treatment safety and efficacy of Firebird SES, especially in the off label indications patients' group in daily practice. At 3 years’ clinical follow-up, a low MACE and acceptable ST rates were found. The safety and efficacy profiles of Firebird SES in treating coronary artery disease patients in daily clinical setting could be proved, although dual antiplatelet therapy longer than 12 months for patients receiving the stent in off label indications might be recommended.

REFERENCES


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