Original article

Sirolimus-eluting cobalt-chromium stents: two-year clinical results from first-in-man study on the Firebird 2™ stent

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Keywords: drug-eluting stents; Firebird 2 stent; coronary artery disease; clinical outcome

Background Drug-eluting stents (DES) have been shown to significantly reduce clinical events and angiographic restenosis in the treatment of coronary artery disease (CAD). This study was conducted to assess the long-term efficacy and safety of the polymer-based sirolimus-eluting cobalt-chromium Firebird 2™ stents in the treatment of patients with CAD.

Methods This first-in-man study using the Firebird 2™ stent is a prospective, historically-controlled multicenter clinical study, which enrolled 67 patients with CAD who were treated with the sirolimus-eluting cobalt-chromium stent (Firebird 2™, Microport Shanghai, Firebird 2 group), compared to another 49 patients treated with a bare cobalt alloy stent (Driver, Medtronic, control group). Continued 2-year clinical follow-up was performed after getting the initial 6-month angiographic and 1-year clinical follow-up. The incidence of major adverse cardiac events (MACE) including cardiac death, reinfarction and target lesion revascularization (TLR) and stent thrombosis were compared between the two groups.

Results All patients in the Firebird 2 group (100.0%) and 48 patients in the control group (98.0%) completed the 2-year clinical follow-up. At the 1-year follow-up the use of the Firebird 2 stent was highly effective, resulting in a significant 94% decrease of TLR (26.5% in the control group and 1.5% in the Firebird 2 group, P<0.0001). A significant difference in TLR was maintained at 2-year follow-up, Firebird 2 group 1.5% and the control group 31.3% (P<0.0001). Between 1- and 2-year post-stenting, no more TLR occurred in the Firebird 2 group compared with two cases in the control group (P>0.05). There was a 1.5% incidence of MACE at 1- and 2-year follow-up in the Firebird 2 group, compared with 26.5% and 33.3% in the control group, respectively (all P<0.0001). The cumulative 1- and 2-year MACE free survival rates were 98.5% in the Firebird 2 group vs 73.5% and 66.7% in the control group (log rank P<0.0001). No case of stent thrombosis occurred during 2-year follow-up in the Firebird 2 group, compared with one case that suffered a definite stent thrombosis in the control group at 19-month post-stenting; this patient presented with unstable angina pectoris and was treated by balloon angioplasty.

Conclusions Compared with the bare cobalt alloy stent, the Firebird 2™ sirolimus-eluting cobalt-chromium stent is safe and effective in treating patients with CAD. The use of this stent was associated with a sustained clinical benefit and significantly lower rate of TLR and MACE up to 2 years post-stenting.

The introduction of drug-eluting stent (DES) has been shown to significantly reduce clinical events and angiographic restenosis in the treatment of coronary artery disease (CAD), as compared to bare metal stents (BMS). The first generation of DES using 316L stainless steel as the stent platform loaded with sirolimus or paclitaxel has been widely used in clinical practice, and recently several clinical studies have shown the safety and efficacy of a new generation of DES with a stent platform modified by cobalt alloy.

The Firebird 2™ stent system (Microport, Shanghai, China) combines the cobalt-chromium coronary stent with the antiproliferative agent sirolimus and a biologically inert styrene-butylenes-styrene (SBS) polymer coating. Results from the first-in-man (FIM) study demonstrated that the Firebird 2™ stent significantly reduced the 6-month in-stent late lumen loss, target lesion revascularization (TLR) rate and one-year clinical major adverse cardiac event (MACE) when compared to the bare cobalt alloy stent (Driver, Medtronic, USA). Given the early results, we evaluated the clinical outcomes up to 2 years post-stenting in order to assess the long-term efficacy and safety of the Firebird 2™ stent platform.
2™ stent in treating patients with CAD.

METHODS

Study design and patient selection
The design and detailed methods of the Firebird 2 FIM study have been reported previously. In brief, 67 patients with de novo or non-stented restenotic coronary lesions with reference diameters between 2.25 mm and 4.0 mm and length <30 mm per lesion were included in the Firebird 2 group. Another 49 patients received Driver stents and were served as controls. Major exclusion criteria included acute myocardial infarction within 1 week, left main or ostial lesions, angiographically visible thrombus containing lesions, a calcified lesion that could not be successfully predilated, bifurcation lesions needing two stents, chronic total occluded lesions, a left ventricular ejection fraction less than 30% and expected life span <12 months. The study was approved by each participating institution’s ethical review committee and all patients provided written informed consents before enrollment.

All patients received aspirin (100 mg/d) and clopidogrel (75 mg/d) at least 2 days before the procedure. Postprocedural dual antiplatelet therapy consisted of 100 mg aspirin daily for all patients indefinitely and clopidogrel 75 mg daily for 6 months in the Firebird 2 group and for 3 months in the control group.

Follow-up and study endpoints
Patients were contacted in the out-patient department (OPD) for an interview or by telephone every month in the first year post-stenting, thereafter every three months. Results of six-month angiographic and one-year clinical follow-up have been reported. In brief, all patients finished one-year clinical follow-up and 86.6% of patients in the Firebird 2 group and 100.0% of the control group received six-month angiographic follow-up. Forty-seven patients (70.1%) in the Firebird 2 group received intravascular ultrasound (IVUS) examination at four to eight weeks, left main or ostial lesions, angiographically visible thrombus containing lesions, a calcified lesion that could not be successfully predilated, bifurcation lesions needing two stents, chronic total occluded lesions, a left ventricular ejection fraction less than 30% and expected life span <12 months. The study was approved by each participating institution’s ethical review committee and all patients provided written informed consents before enrollment.

The primary endpoint of the Firebird FIM study was in-stent late lumen loss at six-month angiographic follow-up with a major secondary endpoint of in-stent percentage of volume obstruction at six-month by IVUS. Other secondary endpoints included angiographic binary restenosis at six months, MACE including cardiac death, recurrent myocardial infarction (MI) or reinfarction and TLR at 1-, 6- and 12-month clinical follow-up and stent thrombosis. At the 2-year clinical follow-up, the prevalence of MACE and stent thrombosis was compared between the two groups. The Academic Research Consortium (ARC) definitions of stent thrombosis were compared between the two groups up to a 2-year follow-up. Briefly, definite stent thrombosis was defined as the presence of an angiographic thrombus in a stent that previously had been successfully deployed. Probable stent thrombosis was defined as unexplained sudden cardiac death or Q-wave MI in the distribution of the stented artery. Possible stent thrombosis was considered in any unexplained death from 30 days after stent implantation.

Statistical analysis
Site monitoring, data management and results analysis were undertaken by an independent organization (Clinical New Drug Base of Ministry of Health, Beijing, China). All analyses were based on the intention-to-treat principle. For continuous variables, a 2-tailed unpaired t test was used. Categorical data were compared by means of the chi-square test or Fisher’s exact test. The rate of endpoints of MACE up to 2 years was estimated with the Kaplan-Meier method, and the difference between groups was estimated with a log-rank test. A P value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 11.0 statistical software (SPSS Inc., USA).

RESULTS

Baseline clinical characteristics
The baseline and procedure characteristics of the Firebird 2 FIM study have been described in detail previously. In brief, the baseline clinical characteristics of the two groups were comparable, though more patients in the Firebird 2 group were previously treated by percutaneous coronary intervention (PCI, 22.4% vs 8.2%, P = 0.0418) and had diabetes mellitus (29.9% vs 12.2%, P = 0.0253). Eighty-eight and sixty-three lesions were treated in the Firebird 2 group and the control group, respectively. The acute lesion, device and procedure success rates were all 100.0% in both groups (Table 1).

Table 1. Baseline characteristics and procedural results in Firebird 2 FIM study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Firebird 2 (n=67)</th>
<th>Control (n=49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (n (%))</td>
<td>16 (23.9)</td>
<td>5 (10.2)</td>
<td>0.0599</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59±1.9.3</td>
<td>59±11.3</td>
<td>0.6845</td>
</tr>
<tr>
<td>Previous MI (n (%))</td>
<td>32 (47.8)</td>
<td>21 (42.9)</td>
<td>0.6020</td>
</tr>
<tr>
<td>Previous PCI (n (%))</td>
<td>15 (22.4)</td>
<td>4 (8.2)</td>
<td>0.0418</td>
</tr>
<tr>
<td>Previous CABG (n (%))</td>
<td>1 (1.5)</td>
<td>2 (4.1)</td>
<td>0.3876</td>
</tr>
<tr>
<td>Diabetes mellitus (n (%))</td>
<td>20 (29.9)</td>
<td>6 (12.2)</td>
<td>0.0253</td>
</tr>
<tr>
<td>Hypertension (n (%))</td>
<td>43 (64.2)</td>
<td>25 (51.0)</td>
<td>0.1570</td>
</tr>
<tr>
<td>Hyperlipidemia (n (%))</td>
<td>25 (37.3)</td>
<td>12 (24.5)</td>
<td>0.1450</td>
</tr>
<tr>
<td>Pre-procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>19.7±10.7</td>
<td>17.6±6.4</td>
<td>0.1387</td>
</tr>
<tr>
<td>RVD (mm)</td>
<td>2.79±0.46</td>
<td>2.98±0.49</td>
<td>0.0175</td>
</tr>
<tr>
<td>DS (%)</td>
<td>66.9±12.3</td>
<td>66.8±10.8</td>
<td>0.9739</td>
</tr>
<tr>
<td>Pre-dilation (n (%))</td>
<td>52 (79.1)</td>
<td>38 (60.3)</td>
<td>0.0800</td>
</tr>
<tr>
<td>Post-procedure (In-stent)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DS (%)</td>
<td>14.8±5.1</td>
<td>13.5±4.9</td>
<td>0.1419</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>2.69±0.43</td>
<td>2.82±0.49</td>
<td>0.0936</td>
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</table>

MACE
Clinical follow-up was available in all patients in the Firebird 2 group (100.0%) and 48 patients in the control group (98.0%) at 2 years after stent implantation. The incidence of recurrent angina pectoris was similar between
Table 2. MACE rate at 2-year follow-up (n (%))

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>6-month Firebird 2 group (n=67)</th>
<th>6-month Control group (n=49)</th>
<th>1-year Firebird 2 group (n=67)</th>
<th>1-year Control group (n=49)</th>
<th>2-year Firebird 2 group (n=67)</th>
<th>2-year Control group (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q wave</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Non-Q wave</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>1 (1.5)</td>
<td>6 (12.2)</td>
<td>1 (1.5)</td>
<td>12 (24.5)</td>
<td>1 (1.5)</td>
<td>13 (27.1)</td>
</tr>
<tr>
<td>PCI</td>
<td>1 (1.5)</td>
<td>6 (12.2)</td>
<td>1 (1.5)</td>
<td>13 (26.5)</td>
<td>1 (1.5)</td>
<td>16 (33.3)</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.0001 vs Firebird 2 group.

the two groups (9.0% in the Firebird 2 group and 14.3% in the control group, \( P=0.38 \)). The cumulative MACE and TLR rates at the 2-year follow-up were significantly reduced in the Firebird 2 group, which was consistent with the 1-year follow-up results. The cumulative 1- and 2-year MACE free survival rates were, respectively, 98.5% and 98.5% in the Firebird 2 group, 73.5% and 66.7% in the control group (Figure 1), mostly attributable to a lower number of TLR in the Firebird 2 group.

Death and MI
No one died at 2-year clinical follow-up in either group. In the control group, one patient experienced non-fatal Q-wave MI at 19-month after the index procedure. The 2-year actuarial survival rate free from death and MI between the two groups was similar (100% vs 98.0%, \( P>0.05 \)).

Target lesion revascularization
There were a total of 16 patients who experienced revascularization up to 2 years after the initial procedure. Only one patient in the Firebird 2 group had TLR at the time of the six-month angiographic follow-up, no more TLR was observed from six-month to the 2-year follow-up. Two patients in the control group had TLR between the 1- and 2-year follow-up and they were treated by PCI and coronary artery bypass grafting (CABG) surgery, respectively. Specifically, the 6-month, 1- and 2-year survival rates free from TLR were 98.5%, 98.5% and 98.5% in the Firebird 2 group vs 87.8% (\( P<0.05 \)), 73.5% (\( P<0.0001 \)) and 68.7% (\( P<0.0001 \)) in the control group (Figure 2). The superiority of the Firebird 2 stentTM treatment appeared at six-month post-stenting and persisted up to 2 years.

Antiplatelet therapy and stent thrombosis
Duration of post-stenting dual antiplatelet therapy was similar between the two groups (11.3±4.5 months in the Firebird 2 group and 11.6±8.6 months in the control group, \( P=0.77 \), Figure 3). A subgroup analysis indicated that significantly longer dual antiplatelet therapy was administered in 5 cases of stent malapposition and in 1 case receiving TLR at the 6-month angiographic follow-up compared with the remaining 61 patients in the Firebird 2 group ((20.2±3.4) months and (10.4±3.7) months, \( P<0.0001 \)), and with the patients in the control group ((20.2±3.4) months and (11.6±8.6) months in the control group, \( P=0.02 \), Figure 4).

According to the ARC definition one case of very late definite stent thrombosis occurred at 19 months after the index procedure in the control group (2.1%). The patient had clinically defined unstable angina pectoris and repeated angiography showed stent thrombosis and in-segment restenosis who was treated by DES implanta-
DISCUSSION

The current study demonstrates the efficacy and safety of the Firebird 2™ stent up to 2 years in the treatment of symptomatic patients with *de novo* or non-stented coronary lesions. At 2 years, no death occurred in either the Firebird 2 or control groups. One patient in the Firebird 2 group experienced TLR at six months after the initial procedure but no more TLR or MACE occurred between six-month and the 2-year follow-up. A significant difference was found when comparing the results from the control group where 15 cases of TLR (31.3%) and 16 cases of MACE (33.3%) were recorded in 2 years. The 2-year MACE free survival rates were 98.5% and 66.7% in the Firebird 2 and the control group, respectively (*P*<0.0001). Combining the results from the Firebird 2 FIM study, we concluded here that the Firebird 2™ stent continued to provide event-free clinical efficacy in treating patients with CAD at 2 years after index procedure. The safety of the Firebird 2™ stent treatment was also proved at 2-year clinical follow-up without stent thrombosis; however dual antiplatelet therapy was continued for a median of 12 months ((11.3±4.5) months).

The first generation of DES using 316L stainless steel as the stent platform, including Cypher (Cordis, USA), Taxus (Boston, USA) and Firebird (Microport) stent etc, has demonstrated remarkable efficacy in reducing TLR when compared to BMS in *de novo* coronary lesions, although the long-term efficacy and safety of these stents in treating complex lesions remains controversial. The update of current DES includes stent platform or polymer coating modifications. Several clinical studies using thin-strut bare cobalt alloy stents have shown the advantages of enhanced visibility, deliverability and radial strength and in reducing restenosis when compared with bare stainless steel stents. When compared to the first generation DES, similar clinical results at 9-month follow-up and favorable cost-effectiveness were found in patients treated by cobalt alloy stents. Recently, results from clinical studies using second generation of DES with modified stent platforms of cobalt alloy have been reported. Four-year clinical follow-up results from the ENDEAVOR I FIM study, reported by Meredith et al., showed that the incidence of MACE was 2% at 1-year, 3% at 2-year, 6.1% at 3-year and 7.2% at 4-year follow-up; and there was only one additional case of TLR from 2–4 years. The results from the ENDEAVOR II trial demonstrated the efficacy of the Endeavor stent in reducing target vessel failure (7.9% and 15.1%, *P*=0.0001) and TLR (4.6% and 11.8%, *P*=0.0001) at 9-month angiographic follow-up as compared to the bare cobalt alloy stent. The difference in clinical outcome was maintained at 12 and 24 months (*P*<0.0001). Three-year clinical results from the SPIRIT First study showed a significantly reduced MACE rate in the Xience V stent treated group (15.4% and 26.0%, *P*=0.04) and clinically driven TLR (7.7% and 25.0%, *P*=0.0001) at 9-month angiographic follow-up as compared to the bare cobalt alloy stent. The difference in clinical outcome was maintained at 12 and 24 months (*P*<0.0001). Pooled meta-analysis for SPIRIT II and III studies showed that ischemic TLR and MACE were significantly reduced in the Xience V stent treated group as comparing to the Taxus stent treated group at 9 months post-stenting (2.4% and 5.1%, *P*=0.01; 4.1% and 8.0%, *P*=0.004).

The Firebird 2™ stent combines an improved stent platform with cobalt-chromium alloy and the anti-proliferate drug sirolimus. The initial results from the FIM study have shown significantly reduced late lumen loss ((0.05±0.09) mm vs (0.98±0.61) mm, *P*<0.0001), and a mild neointimal volumetric obstruction percentage of (1.26±1.05)% at 6-month angiographic and intra-vascular ultrasound follow-up and an improved one-year clinical outcome compared with a bare cobalt alloy stent. Two-year clinical follow-up demonstrated the persisting efficacy of this stent with MACE or TLR free survival of 98.5%, which was more favorable than the Endeavor or Xience V stents. The more potent anti-proliferation effect of sirolimus than zotarolimus, which is loaded on the
Endeavor stent, or everolimus, loaded on the Xience V stent, may be the reason. A recent IVUS study by Miyazawa et al showed that the zatarolimus-eluting stent was associated with a significantly greater incidence of neointimal hyperplasia when compared with the sirolimus-eluting stent.

Stent thrombosis, particularly very late stent thrombosis (>1 year following PCI), remains a concern for DES. Although controversies still exist whether or not DES implantation will increase the rate of stent thrombosis as compared to BMS, especially for on-label uses of DES, there is a clear consensus that stent thrombosis is a clinically relevant adverse outcome. Multiple studies have documented a high rate of death or non-fatal MI secondary to stent thrombosis. In the current study, the inclusion of all patients was strictly controlled and met the criteria of on-label use of either the Firebird 2 or the Driver stent. At 2-year follow-up, according to the ARC definition, no stent thrombosis was reported in the Firebird 2 group but one case in the control group had definite stent thrombosis at 19 months post-stenting (2.1%). Although the relationship between stent malapposition and stent thrombosis is still unclear, patients who were found with stent malapposition by IVUS and experienced TLR at 6 months post-stenting in the Firebird 2 group were treated with a longer dual antiplatelet regimen of clopidogrel and aspirin compared to those without stent malapposition or TLR. The extended duration of dual antiplatelet therapy beyond the protocol defined in Firebird 2 group was mainly due to these patients.

In conclusion, the current 2-year clinical follow-up results from the Firebird 2 FIM study proved the efficacy and safety of the Firebird 2™ stent in treating patients with CAD. The device is highly deliverable and has a favorable safety profile with significant anti-restenotic properties and can be strongly recommended as a valuable therapeutic option for patients with CAD in clinical practice. The ongoing results of this FIM study and future trials in high-risk patients will provide further information on clinical outcome, anti-proliferative effects and of this novel stent patient safety.

REFERENCES


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