
**Experience with Paclitaxel-Eluting Infinnium Coronary Stents**

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ORIGINAL CONTRIBUTION

# Experience with Paclitaxel-Eluting Infinnium Coronary Stents

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## ABSTRACT

To investigate the safety and efficacy of the Infinnium Paclitaxel-eluting stents in the treatment of coronary artery lesions, 196 patients with symptomatic coronary disease who received 202 stents at our center from January 2004 to November 2005 were studied prospectively. The primary study endpoint was the incidence of abnormalities on exercise electrocardiograms or cardiac single-photon emission tomography at 6 months, as a noninvasive index of stent reocclusion. Secondary endpoints were the rates of major adverse cardiac events at 1, 3, 6, 9, and 12 months. Stent deployment was successful in 98% of patients. Cumulative major adverse cardiac event rates at the end of 12 months were: cardiac death 1%, myocardial infarction 5% (Q-wave 2.5%, non-Q-wave 2.5%), and repeat revascularization of the stented lesion 3%. The overall major adverse cardiac event rate was 8.1%. There were 6 (3%) stent thromboses; all occurred late after the procedure. In patients with symptomatic ischemic heart disease, the low-cost Infinnium stent proved both effective and safe, with an acceptably low major adverse cardiac event rate.

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## INTRODUCTION

The use, success, safety, and durability of percutaneous coronary interventions to treat ischemic coronary artery disease have increased day by day since 1977.[1,2] Among the developments in this area are stents that release a drug locally into the diseased vasculature, which have revolutionized the practice of interventional cardiology.[3] These devices are designed to minimize the incidence of stent restenosis that may occur with bare metal stents through blockade of different steps of the cell cycle.[4,5] The paclitaxel-eluting stent consists of a bare metal stent coated with multiple layers of polymer and paclitaxel that is gradually released into the vessel wall, leading to microtubule stabilization, arrest of cell mitosis, retardation of cell migration, and immunomodulation in atherosclerotic plaques.[6,7] Some factors involved in stent restenosis are not modifiable, such as patient and lesion characteristics, whereas procedural characteristics may be improved by better implantation techniques and stent design (changes in platform type, carrier, and drug). The success of drug-eluting devices is highly dependent on each component as well as on the interactions among these elements.[8] Infinnium (Sahajanad Medical Technologies, India) is the first Asian-designed stent. It is made from a Millennium Matrix platform coated with a biodegradable polymer-based carrier that elutes paclitaxel (Taxol; Bristol-Myers Squibb). Because the results of experiments in animal models cannot be directly translated to humans, specific clinical trials of safety and efficacy are required for each device.[7] Follow-up of patients to date have required angiography that is known to accentuate the rates of repeat revascularization compared with clinical follow-up alone, thus the true benefit of drug-eluting stents in routine clinical practice is unknown.[3,9] We decided to study all patients undergoing angioplasty with the low-cost Infinnium stent.

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## Patients and Methods

This non-randomized prospective study was performed at Shiraz Shahid Faghihi Hospital on 200 patients undergoing elective angioplasty between January 2004 and November 2005. The protocol was approved by the hospital's ethics committee, and was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent. Patients were eligible if they were ≥ 18-years old and had a diagnosis of symptomatic ischemic heart disease: stable (Canadian Cardiovascular Society class 1–4) or unstable angina and/or objective evidence of myocardial ischemia. Lesions considered for stenting had at least 71% stenosis. The reference vessel diameter was 2.25–3.75 mm, and cumulative target lesion length was 15–30 mm. Patients were excluded if they were younger than 18-years old or pregnant, had a myocardial infarction (MI) within 72 hours before the procedure, unprotected left main coronary artery stenosis (≥ 50%), angiographic evidence of thrombus within the target lesion, poor distal run-off, or intolerance to aspirin, clopidogrel, heparin, or nickel. The 200 patients received 206 stents.

Patients were pretreated with aspirin 325 mg and clopidogrel 600 mg (at least 12 hours earlier). The appropriate stent diameter and length were determined as: diameter (2.25–3.75 mm) of the Infinnium stent to be implanted, aiming for a stent/vessel ratio of 1–1.3:1 prior to stent implantation (using the nominal pressure); and stent length-lesion length of 4 to 8 mm. Angiographic images were recorded according to the angiography laboratory protocol. Lesions were treated using contemporary techniques according to the manufacturer's instructions. Pre-dilatation was advised, but direct stenting was also allowed. After the stent was implanted, further dilatation was performed to ensure that residual stenosis was ≤ 30% with TIMI (Thrombolysis In Myocardial Infarction) grade 3 flow. Treatment with heparin was continued for 12 hours after the procedure. Patients were then prescribed aspirin (80 mg daily) indefinitely and clopidogrel (75 mg daily) for 6 months. They were evaluated at 30 days and at 3, 6, 9 and 12 months. Specific questions were asked about drug compliance and interim angina, which was categorized according to the Canadian Cardiovascular Society classification for stable angina and the Braunwald classification for unstable angina.[10,11] The patients were also monitored for major adverse cardiac events (MACE) and the need for additional revascularization of the same lesion.

At 6 months after the procedure, all patients who could tolerate running on a treadmill underwent an exercise stress electrocardiogram (EKG), except those with an abnormal resting EKG. All patients who had an abnormal exercise test (defined as flat depression of the ST segment 0.1 mV below baseline [i.e., the PR segment] and lasting longer than 0.08 sec) were sent for coronary angiography, even in the absence of symptoms. Patients for whom the treadmill test was equivocal and those unsuitable for exercise testing underwent single-photon emission computed tomography with intravenous technetium-99m sestamibi, preceded by dipyridamole injection. Patients with a positive cardiac scan were subjected to coronary angiography. Coronary angiograms were obtained in multiple views after intracoronary injection of nitrate solution (1/40). Quantitative analyses of all angiographic data before, during, and after the procedure were performed by 2 independent interventionists using a Siemens Koroscope viewer 1997 (Siemens Medical Imaging, Germany). Visual assessments included lesion type according to the American College of Cardiology / American Heart Association classification, ostial involvement, and angulations. Lesion length, interpolated reference diameter, minimal luminal diameter, and diameter of the stenosis were measured before dilatation and at the end of procedure. Any decision to perform further revascularization of the lesion (surgical or percutaneous) after 6 months was based on clinical criteria.

The study was considered complete when all enrolled patients had been followed up for 12 months. The primary endpoint was the rate of positive treadmill EKG or single-photon emission tomography stress tests at 6 months, as a noninvasive index of stent reocclusion. The secondary endpoints were the composite rates of MACE at 1, 3, 6, 9 and 12 months, defined as cardiac death, Q-wave or non-Q-wave MI, target vessel failure and need for another revascularization procedure, and stent thrombosis (early, up to 30 day; late, up to 12 months). Procedural success was defined as deployment of the stent and a final residual stenosis ≤ 30% with TIMI 3 coronary flow and no MACE during hospital stay. Thrombotic stent occlusion was angiographically documented as complete occlusion (TIMI flow 0 or 1) or a flow-limiting thrombus (TIMI flow 1 or 2) of a lesion previously treated successfully.

Descriptive statistics were performed for all relevant variables. Descriptive variables are summarized by number and percentage. Continuous variables are described by the mean ± standard deviation, minimum, and maximum. Event variables, such as MACE, were analyzed using the Kaplan-Meier method.

## Results

Criteria for successful stent deployment were not achieved in 4 patients. The angiographic and procedural success rate was 98% (202/206 stents). There were no cases of repeat revascularization on clinical grounds. Baseline clinical and

Table 1. **Baseline Clinical Characteristics of 196 Patients with an Infinnium Stent**

| Variable | No. of Patients | % |
|---|---|---|
| Age (years) | 55.2 ± 10.30 | |
| Male | 132 | 67.3 |
| Medically treated diabetes | 40 | 20.4 |
| Medically treated hyperlipidemia | 60 | 30.6 |
| Medically treated hypertension | 36 | 18.4 |
| Current smoker | 42 | 21.5 |

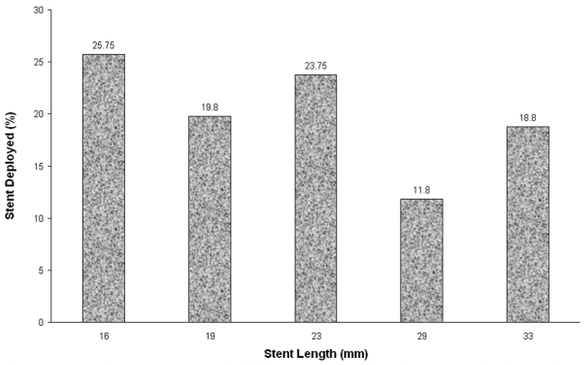


**Figure 1.** Frequency of different length of stents deployed.

Table 2. **Baseline Angiographic Characteristics of 196 Patients with an Infinnium Stent**

| Variable | No. of Patients | % |
|---|---|---|
| Target vessel | | |
| Left anterior descending | 138 | 70.4 |
| Right coronary | 28 | 14.3 |
| Left circumflex | 20 | 10.2 |
| Saphenous vein graft | 10 | 5.1 |
| Number of vessels involved | | |
| Single vessel | 138 | 70.5 |
| Two vessels | 42 | 21.4 |
| Three vessels | 16 | 8.1 |
| Modified ACC/AHA classification | | |
| Type A | 20 | 10.2 |
| Type B1 | 32 | 16.3 |
| Type B2 | 46 | 23.5 |
| Type C | 98 | 50 |
| Reference vessel diameter (mm) | 2.80 ± 0.31 | |
| Baseline lesion characteristics | | |
| Lesion length (mm) | 24.7 ± 10.80 | |
| Ostial involvement | 12 | 6.1 |
| Bifurcation lesion | 24 | 12.2 |
| Total occlusion | 26 | 13.2 |
| Angulations | | |
| Mild | 190 | 96.9 |
| Moderate | 6 | 3.1 |
| PCI for in stent restenosis | 6 | 3.1 |
| Stents per patient | | |
| 1 | 190 | 97 |
| 2 | 6 | 3 |

ACC/AHA = American College of Cardiology/ American Heart Association, PCI = percutaneous coronary intervention.

angiographic characteristics of the remaining 196 patients and 202 stents are shown in Table 1, Table 2, and Figure 1. All of the patients who were alive at the end of 1 year had completed the clinical follow-up. There was a positive treadmill EKG or single-photon emission tomography stress test indicating stent reocclusion in 4 patients at 6 months and in 4 more at 12 months (total, 4.1%).[8] Incidences of MACE are listed in Table 3. The Kaplan-Meier estimate of event-free survival is shown in Figure 2. There were 2 cardiac deaths: a 56-year-old woman died suddenly in her sleep, and a 65-year-old man who had an extensive anterior MI 6 months after angioplasty and angiographic evidence of stent thrombosis, died in hospital before a redo procedure could be performed. Ten patients developed MI (5 had Q-wave MI, 5 had non-Q-wave MI). Of these 10 patients, 7 had occlusion of the stented vessel; in all except one, there was thrombosis in the stent (at 3–9 months after angioplasty).

## Discussion

Due to the economic impact of coronary heart disease and the low peri-procedural complication rate, stenting has been the predominant treatment option. Drug-eluting stents are a novel approach, with local drug delivery inhibiting in-stent restenosis.[5] Series of randomized double-blind trials of slow-release paclitaxel-eluting stents for de-novo coronary lesions (TAXUS I, V and VI) were conducted to collect data on the TAXUS stents in different coronary beds.[8,12,13] However, not all stent designs have been sucessful.[14,15] Both the drug and the delivery vehicle must fulfill pharmacological, pharmacokinetic, and mechanical requirements before use. Furthermore, the cost of the currently marketed drug-eluting stents has been perceived as a major limitation to more widespread use.[16] Analyses from the TAXUS IV trial indicated that paclitaxel-eluting stents led to substantially reduced need for repeat revascularization, while increasing 1-year costs only modestly; but significant price reductions are still needed.[17]

Our results compare favorably with those of the TAXUS study, with lower rates of MI (4% vs 5.4%), repeat revascularization (2.5% vs 8.6%), and MACE (7% vs 15%) at the end of the 9th month. This was gratifying, especially because a large proportion of stents were

Table 3. **Major Adverse Cardiac Events during Follow-up of 196 Patients with an Infinnium Stent**

| Major Adverse Cardiac Event | 30 Days | 3 Months | 6 Months | 9 Months | 12 Months |
|---|---|---|---|---|---|
| Cardiac death | 0 | 0 | 1 (0.5%) | 2 (1%) | 2 (1%) |
| Q-wave myocardial infarction | 0 | 1 (0.5%) | 3 (1.5%) | 5 (2.5%) | 5 (2.5%) |
| Non-Q-wave myocardial infarction | 0 | 1 (0.5%) | 2 (1%) | 3 (1.5%) | 5 (2.5%) |
| Coronary bypass grafting | 0 | 0 | 2 (1%) | 3 (1.5%) | 4 (2%) |
| Repeat angioplasty | 0 | 0 | 1 (0.5%) | 2 (1%) | 2 (1%) |
| Stent thrombosis | 0 | 1 (0.5%) | 2 (1%) | 4 (2%) | 6 (3%) |
| Event-free survival | 196 (100%) | 194 (98.9%) | 86 (94.9%) | 182 (92.8%) | 180 (91.9%) |
| Total major adverse cardiac events | 0 | 2 (1%) | 10 (5%) | 14 (7%) | 16 (8.1%) |
| Positive stress test | 0 | 2 (1%) | 4 (2%) | 6 (3%) | 8 (4%) |

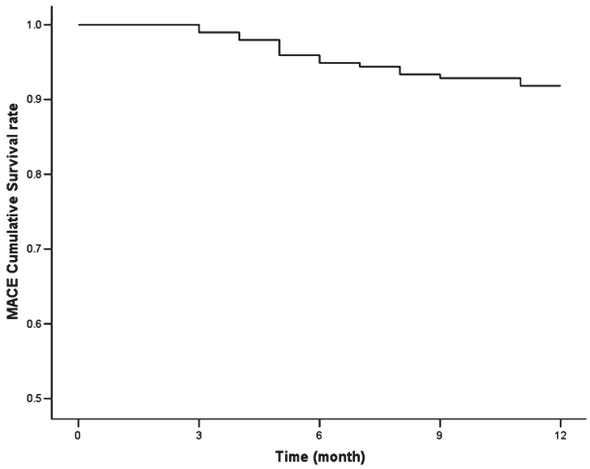


**Figure 2.** Kaplan-Meier estimate of the major adverse cardiac event MACE-free survival rate.

deployed in complex coronary lesions (73.5% type C and B2 lesions; mean lesion length: 24.72 vs 17.3 mm in the TAXUS study).[12,13] However, more stent thromboses (2% vs 0.7%) and cardiac deaths (1% vs 0.5%) were observed. The results of treatment in the subgroup of 40 diabetic patients were interesting as just 2 (5%) patients needed revascularization during the 12 month follow-up. Late stent thrombosis was of some concern. There was a 1% incidence of stent thrombosis in the first 6 month, but an additional 2% occurred when clopidogrel discontinued. However, this trial was not powered to investigate the incidence of stent thrombosis, which would require a randomized trial of 10,000 to 20,000 patients (assuming frequency of 1%).[18]

Another issue is the impact of routine angiographic follow-up on the assessment of the clinical benefits of paclitaxel-eluting stents. Several studies have shown that rates of repeat revascularization increased substantially when patients were subjected to mandatory angiographic follow-up because of "oculostenotic reflex".[17] Thus economic analysis derived from clinical trials that incorporate angiographic follow-up in a high proportion of patients may underestimate the clinical benefits of drug-eluting stents compared to that observed in clinical studies (such as ours) that adjudicate coronary angiography and repeat angioplasty according to clinical findings.[18] Most studies on the Infinnium coronary stent were conducted on approximately 100 patients with descriptive results, on simple coronary lesions, with a fraction of these patients followed up for a short time.[19] They showed easy deployment and promising results with low stent restenosis after 6 months. However, they did not evaluate results in more complex coronary anatomy or the longer-term problems such as late stent thrombosis.

Several limitations of this study should be acknowledged. First is the absence of a control group (for example, Matrix bare-metal stents which have the same platform) to compare the endpoints. Second, the registry is underpowered to examine low-frequency adverse events such as death and stent thrombosis. Third, further studies are required to address patients and lesion excluded from this study, such as acute MI. This study extends the applicability of the paclitaxel-eluting Infinnium coronary stent as a cost-effective treatment for coronary artery disease. Extended follow-up of 5–10 years is required to confirm the safety of Infinnium stents in terms of late thrombosis, acquired malposition, and changes to the vessel wall.

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