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TWO YEAR CLINICAL OUTCOMES AFTER SIROLIMUS-ELUTING STENT IMPLANTATION FOR THE TREATMENT OF CORONARY ARTERY DISEASE

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Abstract

Background Coronary artery stents are known to reduce rates of restenosis after coronary stenting, but it is uncertain how long this benefit is maintained. Clinical data has raised concerns that drug-eluting stents are associated with increased rates of late stent thrombosis, death or myocardial infarction.

Objectives To evaluate the safety and reliability of sirolimus-eluting stents in real-world practice out to two years.

Methods From January 2008 to June 2008, 30 patients were enrolled in the study after implantation of one or more sirolimus-eluting stents. We evaluated clinical follow-up information for up to two years after the implantation of Cypher® Select stents in 30 patients with 35 lesions.

Results Mean patient age was 62.33 +/- 10.99 years, 7 percent were diabetic and 30 percent presented with acute myocardial infarctions. The procedure's success rate was 100 percent for the sirolimus-eluting stent implantation, and follow-up rates were 100 percent. Mean total stent length was 22.32 +/- 6.63 mm, with 13 percent receiving more than one stent. Two year freedom from mortality, myocardial infarction, target vessel revascularization and stent thrombosis was 100 percent. Dual antiplatelet therapy was taken by 100 percent at 1 month, 53 percent at 6 months, 40 percent at 1 year and 0 percent of patients at 2 years. The rate of survival free of myocardial infarction, bypass surgery and repeated angioplasty for stented lesions was 100% at two years.

Conclusions Treatment of lesions with sirolimus-eluting stents is associated with a sustained clinical benefit two years after device implantation.

Keywords

Coronary artery disease; sirolimus-eluting stents; cypher select.

INTRODUCTION

Several pivotal clinical trials have shown that the use of drug-eluting stents (DES) is associated with significant reductions in risks of restenosis and the need for target lesion revascularization as compared with use of the earlier bare metal stents (BMS) [1]. The initial clinical data on DES focused on short-to-medium-term efficiency in reducing restenosis and revascularization, but had insufficient power and duration to assess the incidence of less frequent adverse events such as death [2].

Although the use of stents to treat coronary artery disease (CAD) has soared during the past decade thanks to novel equipment and new implant techniques, clinical data has raised concerns around the safety of DES and their risk of post procedure complications. Some longer-term studies have shown that DES, as compared with bare-metal stents, are associated with increased rates of late stent thrombosis, death or myocardial infarction [3, 4]. On the other hand, the data presented from the RAVEL trial, which was the original trial reporting a remarkable decrease in the rate of restenosis with DES, the long-term incidence of death or heart attack was not significantly different between DES and bare metal stents [5].

Stent thrombosis is a rare complication following stent implantation and is associated with a high morbidity and mortality [6]. Reports from clinical registries [7] and clinical trial consor-

tiums [8] with longer-term-follow up data have suggested the possibility of a higher rate of late stent thrombosis, which might diminish the relative benefit of DES. It has been proposed that the occurrence of late clinical events may be due to delayed arterial healing after implantation of DES [9].

Dual antiplatelet therapy with aspirin and plavix is currently the standard therapy after coronary stent implantation to prevent a life-threatening stent thrombosis. The prolonged use of plavix greatly reduces the risk of late thrombosis in DES, but plavix itself poses problems. Aside from the expense by the long-term use of this drug, there is the risk of bleeding complications.

CYPHER® stents are DESs designed to reduce in-stent stenosis. The CYPHER® Stent releases a unique anti-rejection-type medicine, sirolimus, into the artery wall over a period of 90 days. Sirolimus is released from a bio stable polymer into the artery wall around the stent to help limit the normal overgrowth of tissue as the healing process takes place. Eighty per cent of the sirolimus is released during the first 30 days. The rest is released by the end of 90 days. Sirolimus is a naturally occurring substance that reduces the reproduction of tissue that make-up the bulk of restenosis. Major hallmarks of sirolimus action include inhibition of smooth muscle cell proliferation and migration, immunosuppressive effects and a cytotoxic mode of action by inhibiting early cell cycle phase progression in G₁ by a physi-

ological mechanism ^[2]. The Cypher[®] stent received Conformite European Mark approval in Europe in April 2002, and approval by the U.S Food and Drug Administration in the United States in May 2003.

The concern is that DES might actually worsen, rather than improve long term prognosis. Therefore, this study was designed to evaluate the safety and reliability of sirolimus eluting stents (SES) in daily medical practice out to two years.

METHODS

Ethical Approval: Ethical approval for this study was obtained from the Durban University of Technology Ethical Committee. All patients signed written informed consent before enrolment.

Study Population: Thirty patients with signs and symptoms of CAD were recruited for this study from the department of cardiology at Entabeni Hospital in Durban South Africa. Inclusion criteria included patients implanted with a sirolimus-eluting stent, while exclusion criteria included patients who had a non-cardiac coexisting condition that resulted in a life expectancy of less than one year and patients participating in another drug or coronary device study.

Methods: Electrocardiography, serum levels of cardiac enzymes and coronary angiography was performed to detect ischaemia or infarction.

Percutaneous Coronary Intervention (PCI): Postdilatation was performed as necessary. The stent size and inflation pressure were at the operator's discretion. Demographic, clinical, lesional and procedural data were recorded at the time of catheterization. Age, gender, blood pressure, left ventricular ejection fraction, multivessel disease, previous revascularisation, as well as vessel stented, reference vessel diameter and lesion length before stenting, maximal balloon pressure, were variables included in the list. In addition, a specific reason for stenting and the number of stents implanted was recorded. Multiple stents was defined as the placement of more than one stent unit.

In keeping with the exclusion criteria from the pivotal trials, off-label indications included acute myocardial infarction, left ventricular dysfunction <30 percent, stented length >30 mm, stent diameter <2.5 mm or >3.75 mm, PCI of >1 lesion, and intervention to the left main coronary artery, bypass graft, chronic total occlusion, restenosis, or bifurcation lesion ^[10]. Procedural success was defined as the successful deployment of the stent, resulting in stenosis of less than 20 percent as measured by quantitative coronary angiography. Clinical success was defined as procedural success with no major in hospital complications, such as death, myocardial infarction or the need for bypass surgery ^[11].

Anticoagulant Therapy: After stent implantation, patients were commenced on a loading dose of 300 mg plavix. All patients were advised to maintain daily aspirin 81 mg indefinitely and plavix 75 mg daily for at least 6 months after stent implantation. Patients also received their standard pharmacologic therapy (e.g. statins, beta-blockers or angiotensin-converting-enzyme inhibitors, as appropriate).

Follow up: Clinical follow-up was made regularly at six month intervals for every patient. Patients were monitored for the possible interim development of angina or major adverse cardiac

events (MACE). MACE included death, myocardial infarction, stent thrombosis or repeated revascularizations. Data pertaining to patients' clinical status, all interventions and outcome events were recorded. If any antiplatelet medication had been discontinued, an attempt was made to determine the specific timing of this action.

The success or failure of use of sirolimus-eluting stents was determined by whether or not the target vessel needed repeated revascularization after two years achieved via repeated PCI or coronary artery bypass graft CABG surgery.

To assess safety of sirolimus-eluting stents, the primary clinical end points was major adverse cardiac events, including death, myocardial infarction, stent thrombosis and target lesion revascularization (TLR). All deaths, regardless of cause, were included. The diagnosis of myocardial infarction was based on the universal definition of myocardial infarction ^[12].

Stent thrombosis was defined as the definite occurrence of a thrombotic event according to the Academic Research Consortium classification ^[13]. Stent thrombosis cases were categorized according to the timing of occurrence into acute (<24 hrs after stent implantation), subacute (1-30 days), or late (1-24 months) ^[14]. Target lesion revascularization was defined as either percutaneous intervention or surgical revascularization (CABG) of the stented epicardial vessel. In hospital events were included in the analysis of follow-up events.

Patients who did not complete follow-ups were excluded from the study.

Statistical analysis: Statistical analysis was carried out with the use of Microsoft Excel 2007. The effectiveness analysis and the safety evaluation were performed on an intent-to-treat population. Descriptive statistics were presented as mean and standard deviations. Categorical variables were summarized as frequencies and percentages.

RESULTS

Demographic Data: The patients' mean +/-SD age was 62.33+/-10.99 years with a range of 31 to 75 years. Eighty three per cent were males and 17% were females.

Fifty three per cent of patients had hypertension and seven per cent had diabetes mellitus. Thirteen per cent had a history of myocardial infarction. Seventeen per cent had revascularization of coronary arteries prior to enrolment to the study.

Most patients [n=19, 63%] presented with multivessel coronary disease. The left anterior descending artery [n=18, 53%] was

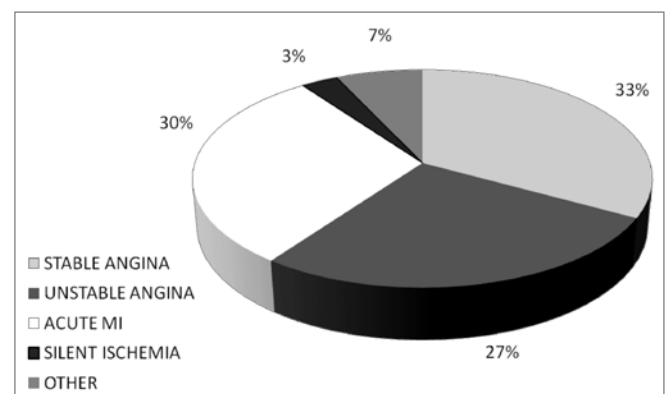


Figure 1: Indications for percutaneous coronary intervention. Acute MI: Acute Myocardial Infarction.

likely to harbour stenosis in the interventional procedures population.

Lesions Treated: A total of 34 coronary lesions were treated with 35 stents during the index procedure. Thirty three per cent of the patients had been hospitalized with acute myocardial infarction at the time of their coronary stent implantation (figure 1). Off label usage was of 60 per cent of the lesions treated (figure 2).

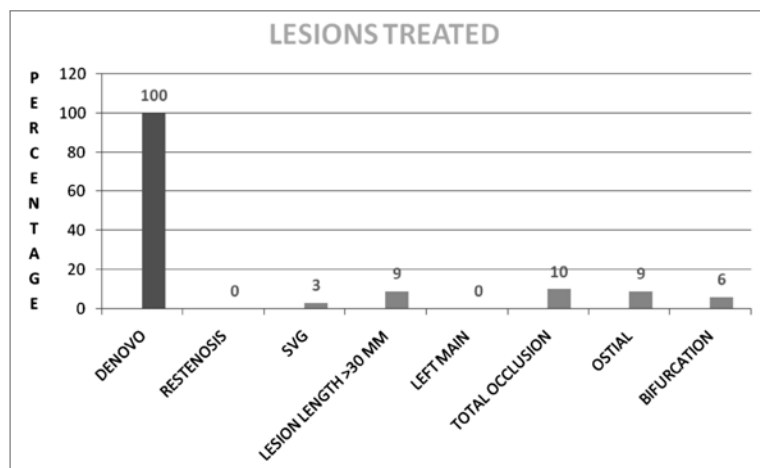


Figure 2: Types of lesions treated with the Sirolimus Eluted Stents. SVG: Saphenous vein graft; Left main: lesions in the left main coronary artery; Ostial: lesions in the ostium of the left main coronary artery; Bifurcation: Lesions at the bifurcation of the left main coronary artery.

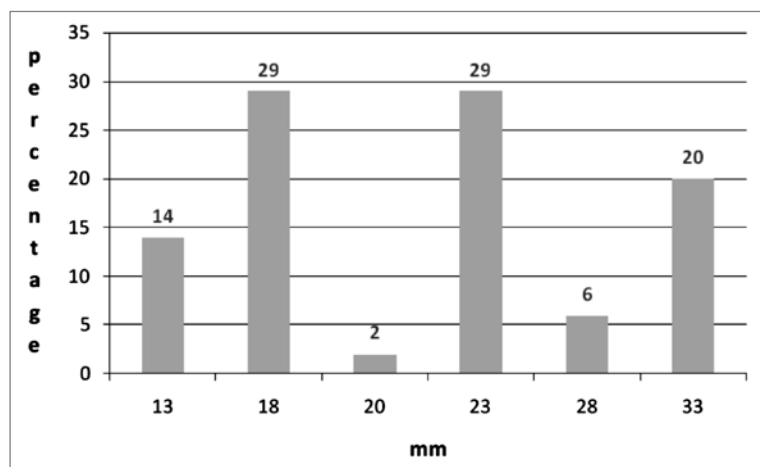


Figure 3: Lengths of Sirolimus-eluting stents used in millimeters (mm).

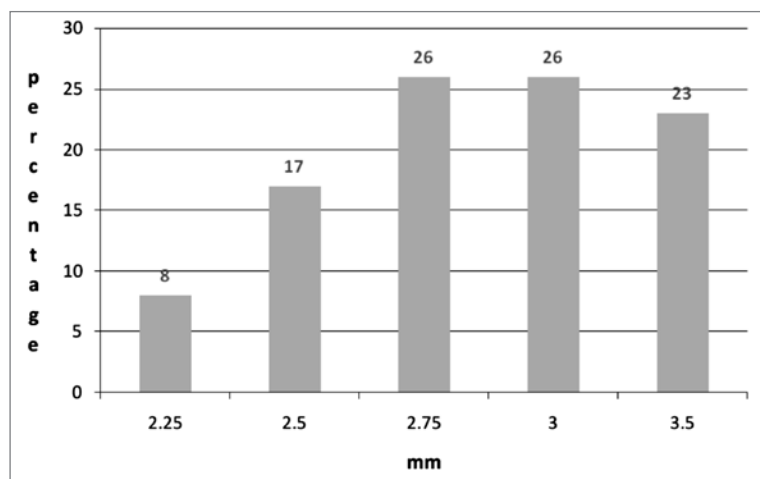


Figure 4: Diameters of sirolimus-eluting stents used in millimeters (mm).

Overall, the average lesion length was 22.32 +/- 6.63 mm and the average reference vessel diameter was 2.77 +/- 0.41 mm. The varying stent lengths and diameters used are shown in figures 3 and 4. All stents were deployed successfully with no major in hospital complications. Approximately 13 per cent of the patients had a single stent implanted in two vessels. Approximately 3 per cent of the patients had a single stent implanted in the proximal and distal segment of an artery.

Clinical Outcomes: Plavix use was maintained in 100 percent, 53 percent, 40 percent and 0 percent of patients at 1 month, 6 months, 12 months, and 24 months, respectively. By 12 months, all 30 patients (100 percent) had discontinued plavix therapy. According to the treatment strategy, 60 percent of patients were on a six month course of dual antiplatelet therapy and 40 percent on a twelve month course. The entire latter 40 percent of the patients adhered to the prescribed plavix therapy through out the year. Overall, fifty three percent of patients on the six month course completed the full duration

There was complete compliance for the total two-year follow-up end points by all 30 patients. No patient experienced recurring symptoms of angina as shown in figure 5. Figure 6 shows that there was a low frequency of adverse outcomes. The survival curves of major adverse cardiac events in figure 7 reveals no incidences of death, myocardial infarction, target lesion revascularization and stent thrombosis during the length of the study period. There was one incidence of a bleeding complication. Seventeen percent of the population experienced adverse events that were not related to the sirolimus-eluting stenting procedure. During the follow-up period, adherence to the assigned study treatment is shown in figure 8.

DISCUSSION

This study was designed to evaluate the two-year clinical outcomes of percutaneous coronary intervention with a sirolimus-eluting stent in everyday medical practice. The main impetus for pursuing a two-year follow-up was to confirm a durable antirestenotic effect of the sirolimus-eluting stent. There were no target lesion revascularizations indicating that the clinical benefit conferred by sirolimus-eluting stents was sustained at two years. Thus, it is unlikely that coronary stenting simply delays clinical restenosis instead of preventing it.

Complete two-year follow-up data for all patients enabled us to estimate event rates precisely at 1 month, 6 months, 12 months and 24 months. The current analysis is meaningful because patients who had received sirolimus-eluting stents had been free of major adverse cardiac events as shown in figure 4.

Other studies using larger populations have indicated that diabetes and acute coronary syndrome are among many factors associated with a higher risk of

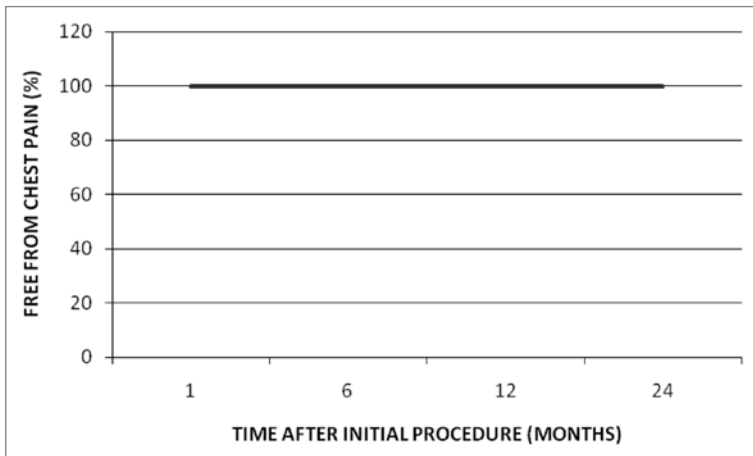


Figure 5: Patients free from ischaemic chest pain over 24 months of clinical followup.

stent thrombosis [15, 16]. In our study population, seven percent of the patients were diabetics and thirty percent presented with acute myocardial infarctions yet there were no incidences of stent thrombosis. In spite of the overall patient and lesion complexity, the study indicated low frequency adverse events with the Cypher® Stent throughout the duration of the study period. The events reported in figure 5 were not related to the sirolimus-eluting stent or the implantation procedure. Although seven per cent of our study population underwent repeated angiograms, the results showed patent stents with no new narrowing.

An observational analysis from the Basel Stent Cost-Effectiveness Trial-Late Thrombotic Events [4], suggested that clopidogrel discontinuation at six months might be associated with higher rates of death and myocardial infarction among patients receiving DES than among patients receiving BMS. This observation is consistent with the reported high rates of death and myocardial infarction among patients with drug-eluting stents in the Duke registry [17] and in the diabetic population [18].

These results have led to uncertainty about the minimal necessary duration of dual antiplatelet therapy after implantation of DES. Dual antiplatelet therapy with aspirin and plavix was the standard therapy after coronary stent implantation to prevent stent thrombosis in the present study. The

duration of the combined antiplatelet therapy is demonstrated in figure 7. Treatment varied from at least four weeks to one year. A variety of procedural and individual factors contribute to the individual patient risk for stent thrombosis. These had to be taken into account to allow for individual recommendation for both the duration and intensity of the antiplatelet therapy. Two patients (seven percent) of patients underwent non-cardiac invasive procedures during the follow-up period. One patient temporarily discontinued plavix for the invasive procedure. The other patient was hospitalized with major bleeding in the fourth month after stent implantation. Plavix was stopped immediately and the patient was treated successfully. Therefore, risk of stent thrombosis should be weighed against the risk for bleeding.

Worldwide, this represents several hundred thousand interventions per year. Previous studies have shown that patients treated for off-label indications have a higher risk of myocardial infarction and stent thrombosis than those with on-label indications [19, 20].

In 2007, an advisory panel from the food and drug administration on circulatory system devices reviewed the broader use of DES in real-world clinical use and the implications of using DES outside of their approved indications. The panel concluded that there was a need for a comprehensive assessment of the safety and efficacy of off-label use of DES [21].

In the present study two patients (seven percent) had stents implanted in de novo coronary bifurcations by one stent strategy. The proximal ramus was stented in a patient who had coronary artery bypass surgery twenty years ago. The second patient presented with an acute infero-lateral myocardial infarction and the

ONE MONTH			SIX MONTHS		
EVENTS	FREQUENCY	PERCENTAGE	EVENTS	FREQUENCY	PERCENTAGE
SES device failure	0	0	SES device failure	0	0
Procedural complications	0	0	Procedural complications	0	0
Bleeding	0	0	Bleeding	1	3
Cardiovascular events	0	0	Cardiovascular events	0	0
Cerebrovascular events	0	0	Cerebrovascular events	0	0
Other adverse events	3	10	Other adverse events	1	3
Coronary angiography	1	3	Coronary angiography	1	3
TWELVE MONTHS			TWENTY FOUR MONTHS		
EVENTS	FREQUENCY	PERCENTAGE	EVENTS	FREQUENCY	PERCENTAGE
SES device failure	0	0	SES device failure	0	0
Procedural complications	0	0	Procedural complications	0	0
Bleeding	0	0	Bleeding	0	0
Cardiovascular events	0	0	Cardiovascular events	0	0
Cerebrovascular events	0	0	Cerebrovascular events	0	0
Other adverse events	1	3	Other adverse events	1	3
Coronary angiography	1	0	Coronary angiography	0	0

Figure 6: Events reported over twenty four months clinical follow-up after implantation of the Sirolimus Eluted Stents.

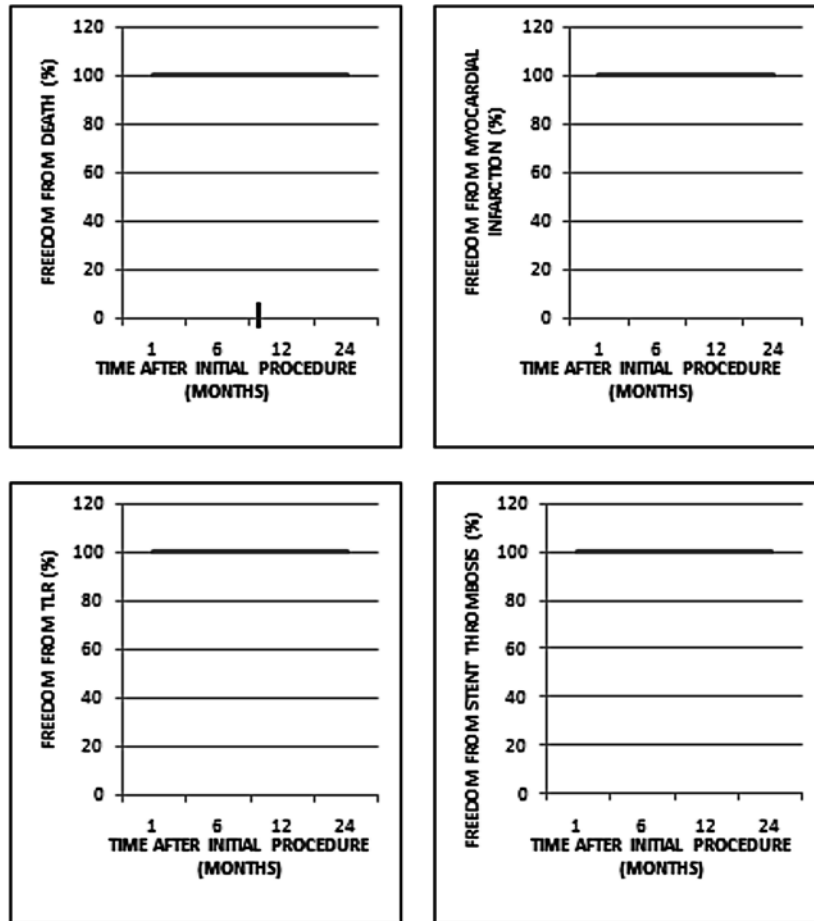


Figure 7: Survival free curves of major adverse cardiac events.

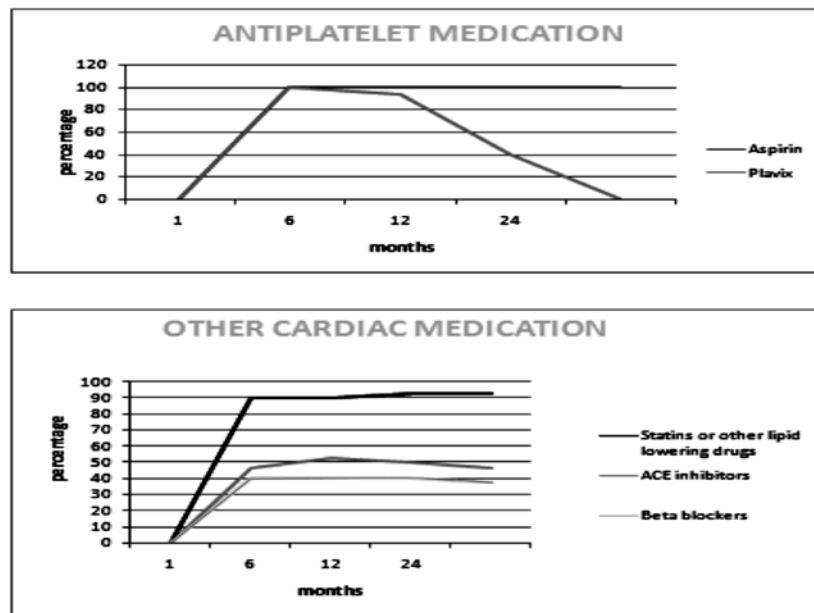


Figure 8: Medications used by the study population over the twenty four months of clinical follow up.

middle circumflex was stented. The findings are similar to those of the ARTS 2 study [22]. The ARTS 2 study not only further confirmed the efficacy of Cypher® in bifurcation treatment but also provided some reassurance that stent thrombosis rates were low (1.5% in ARTS 2) [22].

Also, in the present study, one patient (three percent) had a Cypher Select® sirolimus-eluting stent implanted in a 7 year old

saphenous vein graft. Ten percent of patients had lesions that were chronic total occlusions. Given the fact that our patients tended to have high-risk profiles, our results may correspond with those of previous randomized studies in which relatively high-risk patients showed better clinical outcomes after SES use [23].

CONCLUSION

The results of the study showed that treatment of lesions with sirolimus-eluting stents is associated with a sustained clinical benefit two years after device implantation. Regarding long-term safety the study results revealed no episodes of death, myocardial infarction, and stent thrombosis or target lesion revascularization. Our findings also indicated that off-label use of DES is widespread. Currently we are treating lesions with DES that are far more complex than in the BMS era: more diabetics, older grafts, more complex lesions, smaller diameter grafts, as well as longer and more stents than before. In this study, we have attempted to provide data showing that even in complex lesions, DES maintained their efficacy at two-year follow-up with an acceptable safety profile. Higher initial procedural costs for drug-eluting stents seem to be compensated by lower costs during follow-up. On the basis of the clinical results of this 24-month study, one might reasonably conclude that treating with a sirolimus-eluting stent is safe and effective.

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