THE ASSESSMENT OF TWO YEAR CLINICAL OUTCOMES AFTER STENT IMPLANTATION FOR THE TREATMENT OF CORONARY ARTERY DISEASE

BY

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In the

Department of Biomedical and Clinical Technology

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DECLARATION

I, Ashika Harrypaul declare that this thesis represents research work carried out by myself and that it has not been submitted in any form for another degree at any university or higher learning institution. All information used from published or unpublished work of others has been acknowledged in the text.

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DEDICATION

To my mother, your love, encouragement and support have provided me with the confidence and perseverance necessary to achieve my goals. Your strength will live with me forever. To you, I respectfully dedicate this thesis.

ABSTRACT

Background: The sirolimus-eluting stent (Cypher) was the first approved drug-eluting stent by the Food and Drug Administration in April 2003. This is a stent that is based on a bare-metal stent and is coated with a layer of polymer incorporating sirolimus and releasing it by diffusion. Drug-eluting stents reduced risk of restenosis and repeat revascularization as compared with bare-metal stents. Clinical data has raised concerns that drug-eluting stents are associated with late untoward events.

Objectives: The objective of this study was to test the hypothesis that stenting is safe and effective treatment for coronary artery disease.

Methods and Results: Sirolimus-eluting stenting was performed in 30 patients with 34 coronary lesions. Detailed clinical follow-up data was collected by personal interview or telephone contact at 1, 6, 12 and 24 months. Patients were followed for 2 years for the occurrence of angina and cardiovascular events namely death, myocardial infarction, stent thrombosis and target lesion revascularization. The mean age of the cohort was 62.33±10.99 years; 83 percent were male, 6 percent were diabetic, 53 percent had hypertension. In spite of the overall patient and lesion complexity there were no incidences of major adverse cardiac events and all patients remained angina free out to two years. Dual antiplatelet therapy with aspirin and plavix varied from at least four weeks to one year. One patient had a bleeding event.

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

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DEFINITION OF TERMS

Coronary Artery Disease (CAD)

Coronary artery disease occurs when the arteries that supply blood to the heart muscle become hardened and narrowed. The coronary arteries harden and narrow due to buildup of plaque on their inner walls.

Angina

A recurring distressing pain of the chest that may extend from behind the sternum to the arms, neck and jaws. It is caused by insufficient supply of blood to a portion of the heart.

Myocardial infarction

A condition caused to myocardial tissue when acutely deprived of oxygenated blood, and if not immediately corrected, resulting in necrosis.

Percutanous Transluminal Coronary Angioplasty (PTCA)

Angioplasty is a technique that is used to dilate an area of arterial blockage with the help of a catheter with an inflatable, small, sausage-shaped balloon at its tip.

Coronary Artery Bypass Grafting (CABG)

Coronary artery bypass surgery is a time-tested procedure used to "detour" blood flow around blocked arteries. All forms of bypass surgery involve the removal of a "clean" vessel (graft) from the chest, arm, or leg, and attaching it to the areas around the blocked artery in order to restore blood flow.

Coronary Stenting

Stents are fine wire mesh tubes or stainless steel metal plates. They are mounted on an angioplasty balloon catheter that is inflated to lock the stent in place against the arterial wall.

Drug-eluting Stent (DES)

Drug eluting stents are drug-coated stents. The stent slowly release a drug, and has been shown in clinical studies to significantly reduce the rate of re-blockage that occurs with bare metal stent and angioplasty procedures.

De Novo

The Latin expression *de novo* literally means something akin to "from the beginning" or "anew". When used in reference to a coronary artery disease, it refers to the first occurrence of a lesion in the artery.

LIST OF ABBREVIATIONS

CAD: coronary artery disease

CABG: coronary artery bypass grafting

PTCA: percutanous transluminal coronary angioplasty

BMS: bare metal stent

DES: drug eluting stents

SES: sirolimus-eluting stents

RCA: right coronary artery

LAD: left anterior descending artery

CX: circumflex

Diag: diagonal

PDA: posterior descending artery

OM: obtuse marginal

TLR: target lesion revascularization

HR: heart rate

AO: aortic pressure

LVEF: left ventricular ejection fraction

ECG: electrocardiogram

FDA: Food and Drug Administration

MI: myocardial infarction

PCI: percutaneous coronary intervention

ACE: angiotensin-converting-enzyme

CHAPTER ONE

INTRODUCTION

The treatment of coronary artery disease (CAD) has evolved over last the few decades, especially with the advent of percutaneous coronary intervention. Balloon angioplasty and coronary stenting has revolutionized our current perspective of stable and unstable CAD management. In-stent restenosis is a significant complication associated with the use of bare-metal stents (BMS). The recognition of this important adverse event led to the development of drug-eluting stents (Baim, Kuntz and Popma, 2008). The initial drug-eluting stents (DES) consisted of the same metal framework as the previous bare-metal stent however they were coated with antiproliferative agents such as sirolimus or paclitaxel.

After their introduction, DES dramatically reduced rates of restenosis compared with BMS, leading to an increased confidence to use percutaneous coronary intervention to treat complex lesions such as long lesions, bifurcation lesions, multivessel- disease, chronic total occlusions and lesions involving the left main stem (Kastrati, Mehilli, Pache, Kaiser, Valgimigli, Kelbaek, Menichelli, Sabate, Suttorp, Baumgart, Seyfarth, Pfisterer and Schomig, 2007). The early promising results with DES in terms of reduced restenosis were tempered by initial reports of stent thrombosis occurring in patients many months, and even years, after the index percutaneous coronary intervention (McFadden, Stabile, Regar, Cheneau, Ong, Kinnaird, Suddath, Weissman, Torguson, Kent, Pichard, Satler, Waksman and Serruys, 2004; Liistro and Colombo, 2001; Kerner, Gruberg, Kapeliovich, and Grenadier, 2003). These initial anecdotal reports were supported by subsequent studies reporting an incidence of stent thrombosis from 0.2 percent in postmarket surveillance registries (Gershlick, Guagliumi, Guyon, Lotan, Schofer, Seth, Sousa, Wijns, Berge, Deme, Stoll and Urban, 2006) to over 0.5 percent in trials of multivessel percutaneous coronary intervention (Iakovou, Schmidt, Bonizzoni, Ge, Sangiorgi, Airoldi, Stankovic,

Chieffo, Montorfano, Carlino, Michev, Corvaja, Briguori, Gerckens, Grube and Colombo, 2005; Park, Park, Park, Lee, Kim, Lee, Hong, Kim and Park, 2006; Kuchulakanti, Chu, Torguson, Ohlmann, Rha, Clavijo, Kim, Bui, Gevorkian, Xue, Smith, Fournadjieva, Suddath, Satler, Pichard, Kent and Waksman, 2006).

In addition, concerns were raised over DES safety following studies that suggest that DES use was associated with an increased risk of death and myocardial infarction (Lagerqvist, James, Stenestrand, Lindbäck, Nilsson and Wallentin, 2007; Nordmann, Briel and Bucher, 2006; Camenzind, Ste and Wijns, 2008; Maluenda, Lemesle and Waksman, 2009). Most importantly, these studies stimulated extensive investigation, debate and research, and subsequent recommendations have followed to try to improve safety and minimize the impact of stent thrombosis (Serruys, and Daemen, 2007; Spaulding, Daemen, Boersma, Cutlip and Serruys, 2007).

Dual antiplatelet therapy with aspirin and plavix is currenty 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. Although the incidence of stent thrombosis can be reduced with the use of aspirin and clopidogrel therapy, there is uncertainty about how long this therapy is needed, and there are concerns about the costs of prolonged dual antiplatelet therapy and the associated risk of bleeding (Grines, Bonow, Casey, Gardner, Lockhart, Moliterno, O' Gara and Whitlow, 2007; Eisenstein, Anstrom, Kong, Shaw, Tuttle, Mark, Kramer, Harrington, Matchar, Kandzari, Peterson, Schulman, and Califf, 2007; Spertus, Kettelkamp, Vance, Decker, Jones, Rumsfeld, Messenger, Khanal, Peterson, Bach, Krumholz and Cohen, 2006; Iakovou, Schmidt, Bonizzoni, Ge, Sangiorgi, Airoldi, Stankovic, Chieffo, Montorfano, Carlino, Michev, Corvaja, Briguori, Gerckens, Grube and Colombo, 2005; Pfisterer, Brunner-La Rocca Buser, Rickenbacher, Hunziker, Mueller, Jeger, Bader, Osswald and Kaiser, 2006).

The main limitation to a more widespread use has been their direct and indirect cost. These stents are more expensive than BMS and concerns with the risk of late stent thrombosis have prolonged the duration of dual anti-platelet therapy. In this era of cost containment and economic rationalism, the use of such technical advances remains constrained. Although coronary stenting is generally considered the procedure of choice in most patients presenting with single-vessel disease, many patients with multivessel disease are suitable for coronary stenting. The choice of procedure is often the discretion of the interventional cardiologist and is based on a number of factors including patient preferences, clinical and morphologic characteristics of the vessel lesion, and their relative costs. The cost/benefit ratio of stenting is determined primarily by the increasing need for revascularization. Re-blockages require patients to return to the hospital for additional procedures which potentially include coronary artery bypass surgery. The Basel Stent Kosten-Effektivitaets Trial (BASKET) documented the unfavourable incremental cost-effectiveness ratio for DES versus BMS if all patients were to be treated with DES in a real-world setting and the observational Basel Stent Kosten-Effektivitaets Trial - Late Thrombotic Events (BASKET-LATE) follow up demonstrated that late clinical events related to late DES thrombosis is a real and worrisome complication of DES (Pfisterer, Brunner-La Rocca, Buser, Rickenbacher, Hunziker, Mueller, Jeger, Bader, Osswald and Kaiser, 2006). In a country like South Africa with increasing health care costs interfaced with finite medical resources, selecting the most cost-effective revascularization intervention is a key determinant in reducing health expenditures for coronary heart disease.

This was a prospective, study designed to evaluate the safety and reliability of SES out to two years in our medical practice. The increasing use of percutaneous coronary intervention to treat coronary artery disease, and high overall drug-eluting stent usage in percutaneous coronary intervention procedures in our catheterization laboratory ensures that the safety concerns have important far-reaching implications, and warrant careful evaluation and

critical review. The goals of the present research were to measure the clinical outcomes of DES among a representative of patients receiving sirolimus-eluting stents (SES) in our clinical practice. The resulting analyses will better inform our practice patterns overall. Detailed information, including demographic information, disease severity, comorbidity, past medical history, and procedural details were collected. The primary objective determines if the antirestenosis efficacy is maintained. The secondary objectives assess major adverse cardiac events (MACE) of death, myocardial infarction, stent thrombosis and repeat revascularizations. Concerns about antiplatelet therapy, such as, non compliance and the time of development of ischemic events after stenting are also addressed.

CHAPTER TWO

STUDY BACKGROUND AND REVIEW OF LITERATURE

2.1 STUDY BACKGROUND

2.1.1 The Heart

The heart is the organ which pumps oxygen-filled blood to all parts of the body (figure 1). The heart, which is about the size of the first, has a wall which consists mostly of muscle. Blood is pumped from the heart around the body through a transport system of arteries, veins and capillaries. Pulmonary circulation is the transport of blood from the heart to the lungs and back again. Systemic circulation is the transport of blood from the heart to the rest of the body and back. The blood circulation is two closed systems (Phate, 2008).

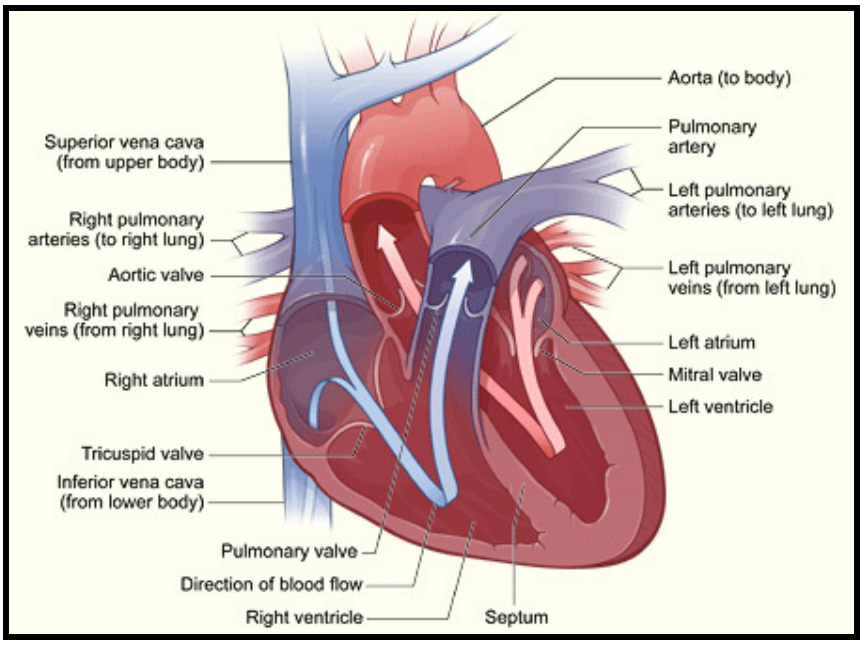

Figure 1: The heart (http://www.medhelp.org/images/heart_interior.gif)

2.1.2 Pulmonary Circulation

The right atrium receives deoxygenated blood from the superior vena cava and the inferior vena cava. The blood then flows into the right ventricle from where it is pumped into the pulmonary artery, which divides into the right and left pulmonary arteries. Blood reaches the lungs via tiny vessels called capillaries, which are porous to gases. The lungs remove carbon dioxide from the blood in the capillaries, replace it with oxygen and return the oxygenated blood to the left atrium of the heart through the four pulmonary veins. The blood is pushed by the contraction of the left atrium through the bicuspid valve into the left ventricle (Phate, 2008).

2.1.3 Systemic Circulation

Systemic circulation is the circulation of blood from the heart to the body. The left ventricle then contracts and pumps the blood through the aorta, which branches to form the ascending and descending aorta, for distribution to all the organ systems. Blood travels throughout the body and returns to the heart through the inferior and superior vena cava (Phate, 2008).

2.1.4 Coronary Circulation

The heart is a muscle which needs the benefits of circulation like every other muscle and organ in the body. The pumping action itself is performed by contraction of the heart muscles surrounding each chamber of the heart. These muscles receive their own blood supply from the coronary arteries, which surround the heart like a crown. The coronary arterial system is a special branch of the systemic circulation. This is the means by which the heart tissues themselves are supplied with nutrients and oxygen and are freed of wastes (Phate, 2008).

2.1.4.1 Right Coronary Artery (RCA)

The RCA arises from the right aortic sinus (figure 2). Near its origin the RCA usually gives off a sinuatrial nodal artery that supplies the sinuatrial node. The RCA then passes towards the inferior border of the heart and gives off acute marginal artery that runs towards the apex. This artery supplies the right ventricle and the apex. After giving off this branch, the RCA turns to the left and continues in the posterior atrioventricular groove. At this point, it gives off the posterior descending artery (PDA) that descends towards the apex. The PDA supplies the inferior surface of the interventricular septum, right ventricle and posterior left ventricle. Near its termination the RCA gives rise to the atrioventricular nodal artery that supplies the atrioventricular node and the Bundle of His (Phate, 2008).

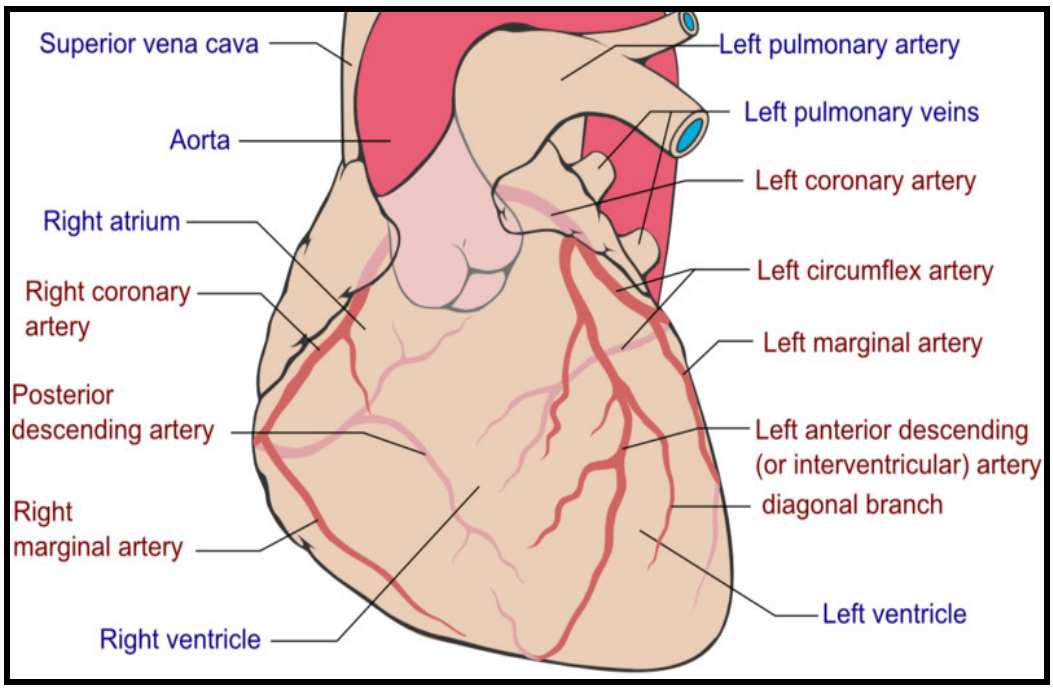

Figure 2: Coronary arteries (http://upload.wikimedia.org/wikipedia/commons/thumb/c/c9/Coronary_arteries.png/800px-Coronary_arteries.pngFile:Coronary arteries.png)

2.1.4.2 Left Coronary Artery (LCA)

The LCA arises from the left aortic sinus and passes between the left auricle and pulmonary trunk to reach the anterior atrioventricular groove (figure 2). In about forty percent of hearts the sinuatrial nodal artery arises from the left system and ascends on the posterior surface of the left atrium to the sinuatrial node. Two bifurcations arise off the main coronary artery. These include the left anterior descending artery (LAD) and the circumflex branch (CX). The LAD courses down the anterior wall of the heart, encircles the cardiac apex and turns around the inferior border and anastomoses with the PDA of the RCA. The LAD supplies the anterior region of the left ventricular wall, part of the right ventricle and the interventricular septum. The LAD also gives rise to the diagonal branch (diag), which descends on the anterior surface of the heart. It normally arises from the proximal LAD and varies in number between 1 and 3. Septal branches (3 to 5) arises at a right angle from the LAD and run within the right half of the septum to the posterior interventricular sulcus. The smaller circumflex branch of the LCA follows the atrioventricular groove around the left boarder of the heart to the posterior surface of the heart. This artery supplies the left atrium and anterolateral region of the left ventricle. A branch of the CX, the obtuse marginal (OM) follows the left margin of the heart and supplies the left ventricle. This artery terminates on the posterior aspect of the heart (Phate, 2008).

2.1.5 Coronary Artery Disease

Disease of the coronary arteries is due to atherosclerosis (Figure 3). Atherosclerosis has been defined as a variable combination of changes of the intima of arteries consisting of a focal accumulation of lipids, complex carbohydrates, blood and blood products, fibrous tissue and calcium deposits, and associated with medial changes (Cowan, Julian and Mclenachan, 2004). A fifty percent reduction in luminal diameter causes a haemodynamically significant stenosis. At this point the smaller distal intramyocardial arteries and arterioles are maximally dilated, and any

increase in myocardial oxygen demand provokes ischemia. CAD gives rise to a wide variety of clinical presentations, ranging from relatively stable angina through to the acute coronary syndromes of unstable angina and myocardial infarction (Clark and Kumar, 2009). The diagnosis of coronary artery disease is made after the patient's medical history is carefully reviewed, a physical examination is performed and the patient's symptoms are evaluated. Test used to diagnose coronary artery disease include:

- Electrocardiogram (ECG)
- Stress test
- Cardiac catheterization
- Imaging tests such as a chest x-ray, echocardiography or computed tomography
- Blood tests

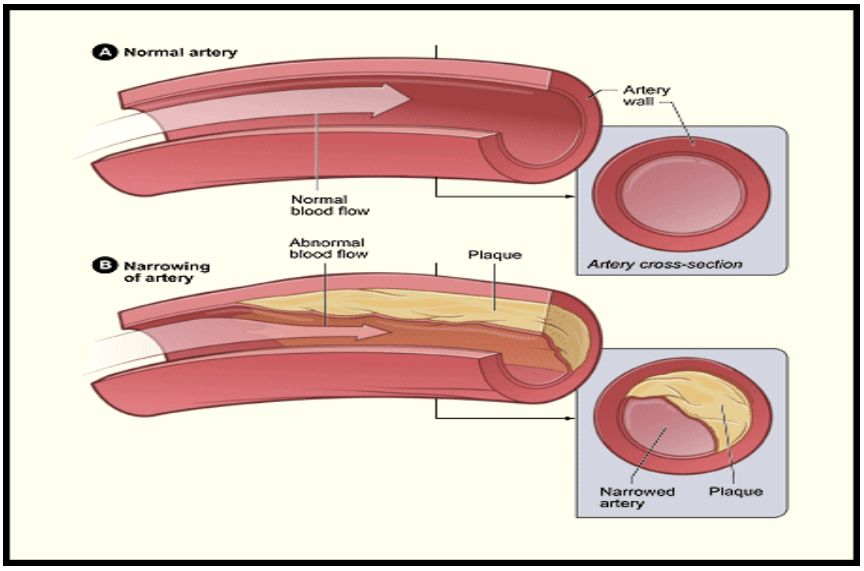

Figure 3: Atherosclerosis (http://nhlibi.nih.gov/health/dci/diseases)

A: shows a normal artery with normal blood flow.
B: shows an artery with plaque buildup.

2.1.5.1 Options of Medical Treatment for CAD

The aim of treatment is to reduce the number of and severity of angina attacks, reduce the risk of death or nonfatal myocardial infarction and improve quality of life. Doctors may prescribe some of the following medicines to control symptoms and, in some cases, slow the progression of CAD:

- Aspirin and other antiplatelet medications help prevent blood clots in coronary arteries.
- Beta-blockers slow the heart rate and lower blood pressure to reduce the amount of work the heart has to do. They also reduce angina.
- Statins lower cholesterol and may reduce risk of a future heart attack.
- Nitrates (nitroglycerin and long-acting nitrates) relieve chest pain and other symptoms of angina.
- Calcium channel blockers slow the heart rate and lower blood pressure to reduce the heart's workload. They also help dilate coronary arteries and reduce angina.
- Ranolazine relieves chest pain when nitroglycerin, beta-blockers, and calcium channel blockers don't work. Unlike other medicines used to treat angina, ranolazine doesn't affect heart rate or blood pressure. Most of the time, it is taken with nitrates or beta-blockers.
- Angiotensin-converting enzyme inhibitors lower blood pressure and reduce the strain on the heart. They may also reduce risk for a future heart attack or heart failure.
- Angiotensin II receptor blockers (ARBs) lower blood pressure and reduce the strain on the heart (*Medications for coronary artery disease,* 2008).

2.1.5.2 Percutaneous Coronary Intervention

The major value of percutaneous or surgical coronary revascularization is the relief of symptoms and signs of ischemic CAD (Smith, Dove, Jacobs,

Kennedy, Kereiakes, Kern, Kuntz, Popma, Schaff, Williams, Gibbons, Alpert, Eagle, Faxon, Fuster, Gardner, Gregoratos and Russell, 2001). The use of percutaneous coronary intervention to treat ischemic CAD has expanded dramatically over the past two decades. The procedural success, safety, and durability of percutaneous coronary intervention have improved dramatically because of continual technological improvements, refinements in periprocedural adjunctive pharmacology and a better understanding of early and late outcomes. These improvements support the expanded use of percutaneous coronary intervention as definitive therapy for many patients with ischemia-producing CAD (Baim, Kuntz and Popma, 2005).

2.1.5.3 Coronary Artery Bypass Surgery

The first procedure to treat blocked coronary arteries was coronary artery bypass grafting (CABG), wherein a section of vein or artery from elsewhere in the body is used to bypass the diseased segment of coronary artery. The technique was pioneered by Argentinian René Favaloro and others at the Cleveland Clinic in the late 1960s. With CABG autologous veins or arteries are anastamosed to the ascending aorta and to the native coronary arteries distal to the area of stenosis. Improved graft survival can be obtained in situ internal mammary and gastroepiploic arteries grafted onto the stenosed artery. A meta-analysis has been performed that demonstrated that compared to medical therapy, CABG significantly improved angina symptoms, exercise capacity and reduced the need for antianginal therapy. In addition, CABG improves 10 year survival in patients with angina, and particularly patients with greater than fifty percent left main stem stenosis and triple-vessel disease with impaired left ventricular function. Operative mortality is well below one percent in patients with normal left ventricular function (Kumar and Clark, 2009).

2.1.5.4 Percutanous Transluminal Coronary Angioplasty (PTCA)

Balloon angioplasty or PTCA was first performed by Andreas Gruentzig in 1977 using a prototype, fixed-wire balloon catheter. PTCA expands the coronary lumen by stretching and tearing the atherosclerotic plaque and vessel wall and, to a lesser extent, by redistributing atherosclerotic plaque along its longitudinal axis (figure 4). PTCA is performed in the catheterization laboratory under local anaesthetic and sedation only. This technique can be performed via the femoral, brachial or radial route. It involves the insertion of a guide catheter usually through the femoral artery which is positioned at the coronary ostium and a steerable guide wire is passed through the stenosis and into the distal segment of the coronary artery. The dilation catheter is then advanced over the wire guide so the balloon is positioned within the stenosis. Then the balloon is inflated, often three or four times, and the atherosclerotic plaque splits at its weakest point. At this point, the dilation catheter and guide wire are removed from the guide catheter and coronary angiography is performed to visualize and evaluate the size and appearance of the enlarged lumen (Giuliani, 1996).

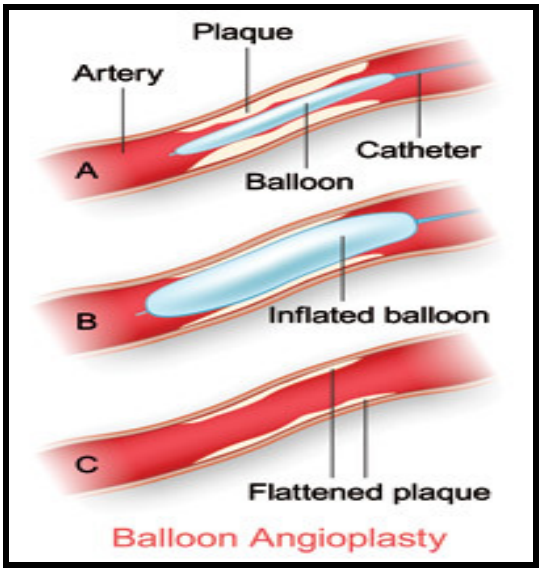

Figure 4: Balloon angioplasty
(http://www.texasheart.org/HIC/Topics/images/fig15_ptca1_3.jpg)

The procedure was initially limited to less than ten percent of patients with symptomatic CAD who had focal noncalcified lesions of a single, proximal coronary vessel, where it was used as an alternative to CABG. As equipment design and operator experience evolved rapidly over the next decade, percutaneous coronary intervention was expanded to a broader spectrum of patients, such as those with multivessel disease, more challenging anatomy, reduced left ventricular function and other serious comorbid medical conditions. Despite these improvements, two major complications limited the widespread use of PTCA. The first was abrupt closure of the treated vessel, which occurred in five to eight percent of cases and required emergency CABG for correction in three to five percent of patients within six to nine months after the initial procedure. The second was the development of symptom recurrence because of restenosis of the treated segment in fifteen to thirty percent of patients within six to nine months after the initial procedure (Baim, 2005).

A series of new coronary devices were developed in the early 1990's (e.g. directional, rotational or extraction atherosclerotic plaque) that sought to improve upon the procedural outcomes achieved with PTCA. However only coronary stenting consistently improved the procedural safety and late clinical outcomes compared with balloon angioplasty in routine patients undergoing percutaneous coronary intervention. Balloon angioplasty has remained an integral component of percutaneous coronary intervention, whether to dilate the vessel prior to stent placement, deploy a coronary stent, or further expand the stent after deployment (Baim, Kuntz and Popma, 2008).

2.2 LITERATURE REVIEW

2.2.1 Coronary Stents

A stent is a stainless tube with slots. It is mounted on a balloon catheter in a collapsed state. When the balloon is inflated, the stent expands and pushes itself against the inner wall of the coronary artery blockage (figure 5). This holds the artery open after the balloon is deflated and removed. The concept of a temporary endoluminal splint to scaffold an occluded peripheral vessel was introduced by Charles Dotter in 1964 but was not practical until the first human coronary implantation was performed in 1986. Self-expanding wire mesh stents were initially used but never attained broad clinical use because of high thrombosis rates. In contrast, a series of balloon-expandable stents has been available in the United States since 1994 (Baim, Kuntz and Popma, 2008).

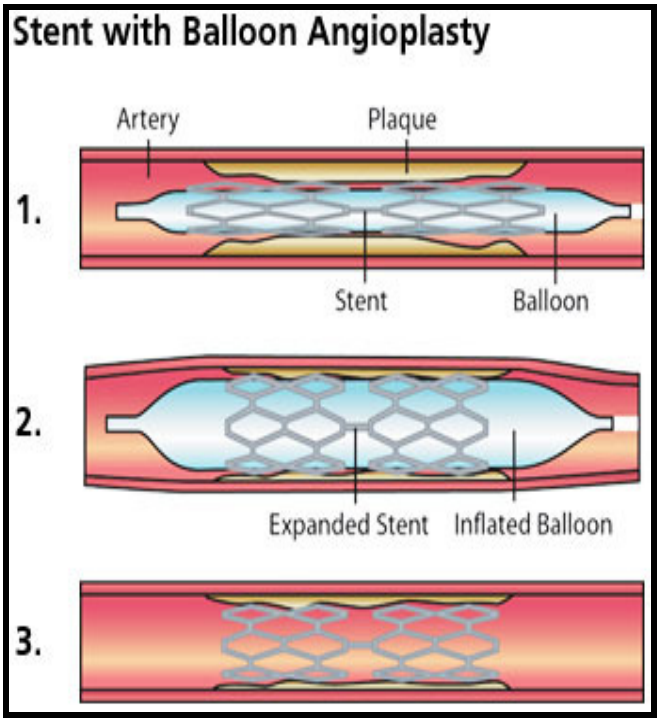

Figure 5: Coronary stenting (http://www.cts.usc.edu/graphics/stent.jpg)

Coronary stents scaffold arterial dissection flaps, thereby lowering the incidence of vessel closure and the need for emergency CABG surgery, and lessen the frequency of restenosis, because of their effect on preventing arterial constriction that is the primary mechanism of restenosis with balloon angioplasty and atherectomy. Despite late clinical improvements compared with balloon angioplasty, restenosis after coronary stent placement occurs in some patients due to excessive intimal hyperplasia within the stent. A number of second-generation balloon-expandable stents were introduced between 1997 and 2003, varying in metallic composition, strut design, stent length, delivery and deployment system, and arterial surface coverage, among other factors. These modifications enhanced flexibility and ease of delivery of the stent, while also improving vessel scaffolding and side branch access. The early use of coronary stents was limited by high subacute thrombosis rates, despite aggressive antithrombotic therapy with aspirin, dipyridamole, periprocedural low-molecularo-weight dextran and an uninterrupted transition from intravenous heparin to oral warfarin (Baim, Kuntz and Popma, 2008). Subacute thrombosis produced profound clinical consequences, resulting in an untoward outcome such as death, myocardial infarction or emergency revascularization in every such patient. Lower frequencies of subacute stent thrombosis have resulted from use of high-pressure stent deployment and with a drug regimen that includes aspirin and a thienopyridine started just after stent placement. While BMS reduce the incidence of angiographic and clinical restenosis compared to balloon angioplasty, angiographic restenosis still occurs in 20 to 30% of patients and clinical restenosis develops in 10 to 15 percent of patients in the first year after treatment (Cutlip, Chhabra, Baim, Chauchan, Marulkar, Massaro, Bakhai, Cohen, Kuntz and Ho, 2004). Restenosis with BMS occurs more often in patients with small vessels, long lesions and in patients with diabetes mellitus, among other factors (Baim, Carrozza, Chauhan, Cohen, Cutlip, Ho, Kuntz and Popma, 2002).

2.2.1.1 De Novo or Restenotic Lesions

Several trials in the 1990s showed the superiority of stent placement over balloon angioplasty. They reduced the restenosis rate from about 50 percent to about 30-35 percent. The Stent Restenosis Study, compared stenting with standard balloon angioplasty in primary focal lesions. The trial clearly demonstrated the efficacy of the stent in reducing the rate of angiographically detected restenosis (Fischman, Leon, Baim, Almond, Bailey, Brinker, Colombo, Clemen, Detre, Ellis, Fish, Goldberg, Heuser, Hirshfeld, Moses, Nobuyoshi, Penn, Rake, Ricci, Savage and Schatz, 1994). In the Benestent trial, there was both angiographic and clinical benefit, as reflected by a reduction in major clinical endpoints, especially repeated coronary angioplasty (Serruys, De Jaegere, Kiemeneij, Belardi, Colombo, Delcan, Emanuelsson, Goy, Heyndrickx, Legrand, Macaya, Marco, Materne, Rutsch, Sigwart and van den Heuvel, 1994). The Restenosis Stent Study (1998), a randomized trial of 383 patients with prior restenosis after PTCA who were assigned to Palmaz–Schatz stenting or repeated PTCA, showed that angiographic restenosis was lower in stent-treated patients than in PTCA treated patients. Target lesion revascularization also occurred less often in patients treated with coronary stents than in patients treated with PTCA alone (Erbel, Haude, Heublein, Höpp, Fischer, Franzen, Jaegere, Probst, Rupprecht, Rutsch and Serruys, 1998).

2.2.1.2 Abrupt or threatened closure after PTCA

Self-expanding and balloon-expanding coiled and slotted tube stents have been used to scaffold coronary dissections in patients with PTCA-induced complications. The clinical use of coronary stents to treat procedural complications has reduced the emergency CABG rates to less than one percent. The use of stents for bailout purposes is uncommon and useful for suboptimal results in smaller vessels or with the development of guiding catheter or guidewire dissections (Baim, Kuntz and Popma, 2008).

2.2.1.3 Saphenous Vein Grafts

Although PTCA of saphenous vein graft lesions is associated with reasonably high procedural success rates, clinical recurrence related to restenosis or progression of disease at other SVG sites is common. The saphenous vein graft de novo trial (1997) randomly assigned 220 patients with de novo SVG lesions to treatment with Palmaz-Schatz stent placement or PTCA alone. Stenting was associated with a higher procedural success rates at the expense of more bleeding events because of the aggressive anticoagulation regiment used in this study. Although restenosis was not significantly lower in stent-treated patients than in PTCA treated patients, freedom from significant cardiac events was better in the stent group. Stents are the preferred therapy in patients with ostial or body SVG lesions (Savage, Douglas, Fischman, Pepine, King, Werner, Bailey, Overlie, Fenton, Brinker, Leon, Goldberg, Heuser, Smalling, Cleman, Buchbinder, Snead, Rake, Safian and Gebhardt, 1997).

2.2.1.4 Total Coronary Occlusions

Percutaneous transluminal coronary angioplasty of chronic coronary occlusions is associated with reduced procedural success, primarily because of failure to cross with a guidewire. Even when crossed successfully, total occlusions have a high incidence of restenotic recurrence, often as recurrent total coronary occlusion. There appears to be no significant benefit of plaque debulking for the treatment of coronary total occlusions. A number of randomized trials have shown the benefit of stent placement over PTCA alone in patients with chronic occlusions. The total occlusion study of Canada trial randomly assigned 410 patients with native coronary occlusions to PTCA or primary stenting with the heparin coated Palmaz-Schatz stent. A reduced binary restenosis rate was found in patients treated with the heparin-coated stent compared with PTCA (Buller, Dzavik, Carere, Mancini, Barbeau, Lazzam, Anderson, Knudtson, Marquis, Suzuki, Cohen, Fox and Teo, 1999). In the stenting in chronic coronary occlusion study (1996), 119 patients with

successful PTCA of chronic coronary occlusion were assigned to no further intervention or to Palmaz-Schatz stent placement. Angiographic restenosis occurred less often in stent-treated patients than in patients receiving no further therapy. Target lesion revascularization was also needed less often in stent-treated patients than in PTCA treated patients. This benefit was sustained at late follow-up (Sirnes, Golf, Myreng, Albertsson, Brekke, Emanuelsson, Endresen, Kjekshus, Molstad and Mangschau, 1996).

2.2.1.5 ST Segment Elevation Myocardial Infarction

Primary stenting confers advantages over PTCA in patients with ST segment elevation myocardial infarction by scaffolding the ruptured plaque and preventing the arterial remodelling that occurs with PTCA (Grines, Cox, Stone, Garcia, Mattos, Giambartolomei, Brodie, Madonna, Eijgelshoven, Lansky, O' Neill and Morice, 1999).

2.2.2 Drug-Eluting Stents

Drug-eluting stents were licensed for use in the United States and Europe on the basis of evidence of a reduced risk of restenosis and repeat revascularization obtained from randomized controlled trials conducted in selected patients (Moses, Leon, Popma, Fitzgerald, O' Shaughnessy, Caputo, Kereiakes, Williams, Jaeger, Kunt and Holmes, 2003; Stone, Ellis, Cox, Hermiller, O' Shaughnessy, Mann, Turco, Caputo, Bergin, Greenberg, Popma and Russell, 2004; United States Food and Drug Administration. Cypher sirolimus-eluting coronary stent on RAPTOR over-the-wire delivery system or RAPTORRAIL rapid exchange delivery system, 2004). The indications for DES use approved by the United States Food and Drug Administration were derived from the inclusion criteria from the pivotal trials. They comprise a de novo lesion ≤30 mm in a native artery, with a diameter of 2.5 mm to 3.5 mm inclusive for the sirolimus-eluting stent. Indications that fulfil the United States Food and Drug Administration criteria are referred to as on label.

2.2.2.1 Sirolimus - First in-human studies

The SES (Cypher) was the first approved DES by the Food and Drug Administration (FDA) in April 2003. This is a stent that is based on a BMS and is coated with a layer of polymer incorporating sirolimus and releasing it by diffusion. The safety and efficacy of SES has been studied in several trials against BMS or paclitaxel-eluting stents in different clinical circumstances. Sirolimus-eluting Bx Velocity stents were first implanted in 45 patients with focal native vessel disease. In-stent minimal lumen diameter and percent diameter stenosis were essentially unchanged from the post procedural study to the 18 to 24 month follow up study. Intravascular ultrasound detected neointimal hyperplasia was virtually absent at 12 months in both groups (Sousa, Costa, Sousa, Abizaid, Seixas, Abizaid, Feres, Mattos, Falotico, Jaeger, Popma and Serruys, 2003).

2.2.2.2 The RAVEL Study

RAVEL study is a landmark study, first double blind, and randomised study conducted in Europe. The randomized study with the Sirolimus-Eluting Bx Velocity Balloon Expandable Stent trial randomly assigned 238 patients with single, primary lesions located in native arteries to treatment with the sirolimus stent or the bare metal stent. During a follow up period of one year, the overall rate of major cardiac events was 5.8 percent in the sirolimus stent group and 28.8 percent in the standard stent group. The rates of deaths were identical in both groups at the end of 1 year (Morice, Serruys, Sousa, Fajadet, Hayashi, Perin, Colombo, Schuler, Barragan, Guagliumi, Molnar and Falotico, 2002). At the end of 5 years, the number of deaths in the sirolimus-eluting stents was much higher when compared to control group. Rate of target vessel revascularisation was significantly lesser in the sirolimus-eluting stents group. Rate of MACE (composite of all cause death, myocardial infarction and target lesion revascularization) was higher in bare metal stent arm, due to high rates of revascularisation. Cause of 6 out of 14

deaths in the sirolimus-eluting stent arm was cardiac versus 6 out of 8 in the control arm (Morice et al, 2007).

2.2.2.3 The SIRIUS Trial

The extent of coronary disease and the complexity of lesions were relatively limited in the RAVEL trial. In contrast, the Sirolimus-eluting stent in de novo native coronary lesions (SIRIUS) trial was a much larger randomized trial from the United States, incorporating what has been described as a “sicker”, more “real world” population. The sirolimus-eluting stent in de novo coronary artery lesions trial included 1058 patients with a lesion length between 15 mm and 30 mm and a reference diameter between 2.5 mm and 3.5 mm and randomly assigned them to treatment with a sirolimus-eluting stent or a bare metal stent. The primary clinical endpoint in the SIRIUS trial was 8 month target vessel failure, defined as target vessel revascularization, death or myocardial infarction and it was reduced from 21 percent in patients treated with bare metal stents to 8.6 percent in patients with sirolimus-eluting stents. Target vessel revascularization was reduced from 16.6 percent with bare metal stents to 4.1 percent in patients treated with sirolimus-eluting stents. Importantly, in the analysis of high-risk subgroups, total lesion revascularization events were significantly reduced in patients with diabetes and in anatomic subgroups including left anterior descending lesions, lesions in small vessels and long lesions. Compared with patients treated with bare-metal stents, patients treated with sirolimus-eluting stents had lower rates of binary angiographic restenosis within the treated segment and within the stent (Moses et al, 2003). Thus, while not as dramatic as the results from RAVEL in terms of absolute restenosis prevention, the results from the SIRIUS trial continue to confirm significant efficacy for the drug-eluting sirolimus stent.

DES were enthusiastically received in 2002 by interventional cardiologists worldwide. By 2003, the mood was tempered following initial reports of thrombosis. A cautionary note was sounded with the description of 4 patients,

more than 300 days after device implantation, who suffered stent thrombosis within two weeks of stopping dual antiplatelet therapy for invasive or operative procedures (McFadden, Stabile, Regar, Cheneau, Ong, Kinnaird, Suddath, Weissman, Torguson, Kent, Pichard, Satler, Waksman and Serruys, 2004). Virmani and colleagues raised mechanistic possibilities with a case report of fatal sirolimus-eluting stent thrombosis 18 months post implantation (Virmani, Guagliumi, Farb, Musumeci, Grieco, Motta, Mihalcsik, Tespili, Valsecchi and Kolodgie, 2004). Histopathology showed evidence of hypersensitivity involving eosinophils, lymphocytes and giant cells. With the known elution kinetics of sirolimus from this platform, they posited a proinflammatory effect of the non-erodible polymer reservoir. Ensuing real-world reports provided conflicting data on the short- and intermediate-term safety of DES. Even though a meta-analysis of randomized studies and registries confirmed the efficacy and safety of DES, these studies were not powered to detect any increase in late-stent thrombosis. Furthermore, in those studies, stent thrombosis was not equal and appropriately defined; more importantly, none of the cited studies included stent thrombosis as a prespecified end point (Bavry, Bhatt, Helton and Kumbhani, 2005). From a prospective cohort, 9-month outcomes in 2229 patients without ST-elevation myocardial infarction who were revascularized using DES was analysed (Airoldi et al, 2005). It determined a 1.3% rate of definite and probable stent thrombosis, higher than that reported from pivotal trials. Ong and colleagues from Rotterdam presented a sequential cohort of 2512 patients treated with BMS or DES (Ong, Hoye, Aoki, van Mieghem, Granillo, Sonnenschein, Regar, McFadden, Sianos, van der Giessen, de Jaegere, de Feyter, van Domburg and Serruys, 2005). Thirty-day rates of stent thrombosis were very similar (BMS 1.4%, SES 1.5%, PES 1.6%).

The four studies that first raised the issues of DES safety were:

- The single-center BASKET-LATE study of 746 unselected patients randomized to either sirolimus-eluting stents or BMS reported a higher

rate of death or myocardial infarction between 7 and 18 months after the index percutaneous coronary intervention with DES compared with BMS (adjusted hazard ratio [HR]: 2.2; p = 0.03). Angiographic late stent thrombosis was more frequent in the DES group (2.6% vs. 1.3%). Overall, the study was underpowered to detect infrequent stent thrombosis events, and limited angiographic evidence was available to confirm that events were actually due to stent thrombosis, although this was a possibility (Pfisterer et al, 2006). With the caveat of limited study size, these investigators raised the possibility that clinicians were trading a reduction in restenosis for higher rates of thrombosis and, possibly, mortality.

- Camenzind and collegues pooled the published data from RAVEL, Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS), E-SIRIUS and C-SIRIUS, which were the four randomized, controlled trials assessing the safety and efficacy of the Cypher® sirolimus-eluting stent (Cordis, NJ, USA), and showed a statistically significant 2.4% increase risk for death and Q-wave MI for SES compared with BMSs (6.3 vs 3.9%; p = 0.03) (Camenzind, Steg and Wijns, 2008) . Criticism was directed at the unusual end point of death and Q-wave myocardial infarction, as opposed to the conventional end points of death and all cause myocardial infarction (Q-wave and non-Q-wave); in fact, non-Q-wave myocardial infarction was significantly lower with sirolimus-eluting stents. Furthermore, the study relied on aggregate trial data, as opposed to patient-level data. A subsequent analysis on the same studies using patient-level data reported no significant difference in death/myocardial infarction between both groups (11.4% SES vs 10.1% BMS; p = 0.4) (James, Stenestrand, Lindback, Lagerqvist, Nilsson and Wallentin, 2009).
- Nordmann and collegues performed a meta-analysis on 17 randomized trials of patients treated with sirolimus-eluting stents, BMS and paclitaxel-eluting stents, and demonstrated a statistically significant increase in noncardiac mortality between 2 and 3 years following sirolimus-elting stent implantation (Nordmann, Briel and Bucher, 2006) Again, criticism

was directed at the reliance of aggregate trial data, as opposed to patient-level data.

- The Swedish Coronary Angiography and Angioplasty (SCAAR) registry initially comprised a cohort of just under 20,000 patients treated with either BMS or DES in Sweden between 2003 and 2004. The initial results at 3 years follow-up demonstrated that the overall rate of death was higher in those receiving a DES (adjusted relative risk: 1.18; 95% CI: 1.04–1.35) (Lagerqvist, James, Stenestrand, Lindbäck, Nilsson and Wallentin, 2007). Interesting results from the extended registry, which included patients treated in 2005, showed a 31% reduction in events during the first 6 months with DES and no difference in events between DES and BMS during long-term follow-up. The exact reason for this so called 'Swedish yo-yo' has not been established; however, of possible significance is the use of DES, which increased from 22 to 53 percent of percutaneous coronary intervention procedures from 2003 to 2005 (Serruys and Daemen, 2007). Most recently, data from the registry, extended to include new patients treated in 2006, and now including just under 48,000 patients, showed a similar long-term incidence of death or myocardial infarction among DES and BMS patients. Furthermore, DES were also shown to have a reduced rate of restenosis among high-risk patients (Farb and Boam, 2007).

In December 2006, the United States Food and Drug Administration convened a panel of cardiovascular experts to review drug-eluting stent safety data. The panel reviewed available data and concluded that there was no additional risk of stent thrombosis in patients treated with DES compared with BMS for 'on-label' indications', however, an increased risk of early/late stent thrombosis, myocardial infarction and mortality existed with the use of DES for 'off-label' indications when compared with 'on-label' indications. The panel recommended increasing dual antiplatelet therapy use to a minimum of 12 months, and concluded by stressing the importance of patient selection, and the need for large, adequately powered studies to investigate the issue

of stent thrombosis (Boam and Farb, 2007). The information for use for the sirolimus–eluting stent states that “indicated use is for disease due to discrete de novo lesions of length less than or equal to 30 mm in the native coronary arteries with a reference vessel diameter greater than or equal to 2.5 mm to less than or equal to 3.75 mm (Cordis Corporation. Cypher sirolimus-eluting stent: essential prescribing information, 2010). Off-label use for the sirolimus-eluting stent is defined as stenting of a restenotic lesion, lesion in a bypass graft, lesion length greater than 30 mm, or reference-vessel diameter less than 2.5 mm or greater than 3.5 mm (Jensen, 2007; Iakovou et al, 2005).

Following on from this call, extensive data from registries, randomized, controlled trials and meta-analysis have been published that demonstrate the overall comparable outcomes between DES and BMS in terms of death and myocardial infarction, at both short and long term follow-up.

Stettler and collegues performed a large meta-analysis of thirty eight DES trials, including over 18,000 patients with follow-up up to four years (Stettler, Wandel, Allemann, Kastrati, Morice, Schömig, Pfisterer, Stone, Leon, de Lezo, Goy, Park, Sabaté, Suttorp, Kelbaek, Spaulding, Menichelli, Vermeersch, Dirksen, Cervinka, Petronio, Nordmann, Diem, Meier, Zwahlen, Reichenbach, Trelle, Windecker, Jüni, 2007). The risk of death was similar between patients treated with sirolimus-eluting stents, paclitaxel-eluting stents and bare-metal stents; the risk of myocardial infarction, although comparable between paclitaxel-eluting stents and bare-metal stents ($p = 0.99$), was significantly lower with sirolimus-eluting stents compared with bare-metal stents ($p = 0.03$).

In March 2007, the New England Journal of Medicine published 5 original papers on the subject of DES thrombosis and safety with overlap of the trials included in the different studies. The studies comparing DES with BMS, encompassing 19 randomized trials, yielded the following findings (Mauri, Hsieh, Massaro, Ho, D’ Agostino, and Cutlip, 2007; Spaulding, Daemen,

Boersma, Cutlip and Serruys, 2007; Stone et al, 2007; Kastrati et al, 2007; Lagerqvist et al, 2007).

- A slightly lower risk for stent thrombosis with DES than with bare BMS before one year, but a significantly higher risk after one year, representing an absolute disadvantage of about 0.5% to 1.0% with drug-eluting stents.
- No difference in stent thrombosis between sirolimus-eluting and paclitaxel-eluting stents.
- Documentation that some drug-eluting stent recipients on long-term dual antiplatelet therapy experienced late stent thrombosis.
- No statistically significant difference in death or myocardial infarction between BMS and either sirolimus-eluting or paclitaxel-eluting stents.
- A marked reduction in target-vessel revascularization with drug-eluting stents.
- A tendency toward higher mortality with sirolimus-eluting stents than with bare metal stents in diabetes patients.

These analyses have confirmed sustained clinical efficacy and acceptable safety profiles with up to four years of follow-up among patients with largely on-label indications. One of the criticisms of early DES trials was that they enrolled stable patients with noncomplex, single de novo lesions. The meta-analyses by Stettler et al (2007), Stone et al (2007) Spaulding et al (2007) and Kastrati et al (2007) included patients who were essentially stable with simple native lesions; the mean lesion length was 23–24 mm, the mean lesion diameter was 2.7 mm, and on average 1.2–1.4 stents were implanted. Stettler and Kastrati did, however, include patients with acute myocardial infarction (<25 percent), and some with chronic total occlusions. Some argue that the comparative outcomes between DES and BMS shown in these studies do not reflect real-world clinical practise in which 60–70% of DES are used in off-label indications, which can be associated with a worse outcome and a higher risk of stent thrombosis (Ko, Chiu, Guo, Austin, Goeree, Cohen,

Labinaz and Tu, 2009). There are no dedicated randomized trials comparing DES for off-label indications to BMS, and data from both registries and subgroups of randomized trials have shown conflicting results.

The results from two registries demonstrate that the 'off-label' use of DES is not associated with an increased risk of death or myocardial infarction at one year compared with BMS ((Ko et al, 2009) and (Marroquin, Selzer, Mulukutla, Williams, Vlachos, Wilensky, Tanguay, Holper, Abbott, Lee, Smith, Anderson, Kelsey and Kip, 2008)). Conversely, the TAXUS® peri-Approval Registry: a Multi-Center Safety Surveillance (ARRIVE) registry of 7500 patients has shown significantly poor outcomes in terms of death ($p < 0.001$), cardiac death ($p < 0.001$), MI ($p = 0.001$) and target lesion revascularization (TLR; $p < 0.001$) using the TAXUS Express paclitaxel-eluting stent for 'expanded use' compared with 'simple use' out to 2-years follow-up (Lasala, Cox, Lewis, Tadros, Haas, Schweiger, Chhabra, Untereker, Starzyk, Mascioli, Dawkins, Baim . 2009).

Similarly, Brodie and collegues reported results from the Strategic Transcatheter Evaluation of New Therapies (STENT) study, which compared outcomes in over 17,000 patients treated with DESs for on- (6063) and off-label (8897) indications, and BMS for off-label indications (2131) at nine months, and two years follow-up. Outcomes were significantly better in terms of death, myocardial infarction and target vessel revascularization for on-label DES use compared with off-label DES use at nine months and two years (Brodie, Stuckey, Downey, Humphrey, Bradshaw, Metzger, Hermiller, Krainin, Juk, Cheek, Duffy, Smith, Edmunds, Varanasi, Simonton, 2008). Furthermore, outcomes among off-label DES patients were significantly better compared with off-label BMS patients Most recently, Kirtane *et al.* have reported the results of an analysis of 9470 patients from randomized, controlled trials, and 182,901 patients from registry data that included patients with both on- and off-label indications. In the randomized studies for both on- and off-label indications, at a median of 2.9 years follow-up (range:

1.5–5.0 years), no significant difference was reported in rates of death or myocardial infarction between DES and BMS. In observation studies at a median of 2.5 years (range: 2.0–4.0 years), there was a significant reduction in death (22%) and myocardial infarction (13%) with DES (Kirtane, Gupta, Iyengar, Moses, Leon, Applegate, Brodie, Hannan, Harjai, Jensen, Park, Perry, Racz, Saia, Tu, Waksman, Lansky, Mehran, Stone, 2009).

2.2.4 Outcomes following Percutaneous Coronary Intervention

Procedural success and complication rates are used to measure outcomes after percutaneous coronary intervention. Early (<30 day) success (e.g. relief of angina, freedom from death, myocardial infarction and urgent revascularization) generally relates to the safety and effectiveness of the initial procedure. Late (30 days to 1 year) success (e.g. freedom from recurrence of angina, target vessel revascularization, myocardial infarction, or death) depends on both clinical restenosis and progressive atherosclerosis at remote sites (Smith, Feldman, Hirshfeld, Jacobs, Kern, King, Morrison, O' Neil, Schaff, Whitlow, Williams, Antman, Adams, Anderson, Faxon, Fuster, Halperin, Hiratzka, Hunt, Nishimura, Ornato, Page and Riegel, 2006).

2.2.4.1 Early Clinical Outcome

Angiographic success after coronary stenting is defined as the attainment of residual diameter stenosis less than 20 percent, which is generally associated with at least a 20 percent improvement in diameter stenosis and relief of ischemia. Procedural success is defined as angiographic success without the occurrence of major complications within 30 days of the procedure. Clinical success is defined as procedural success without the need for urgent repeated percutaneous coronary intervention or surgical revascularisation within the first 30 days of the procedure (Adams et al, 2006). Major complications include death, myocardial infarction or stroke. Minor complications include transient ischemic attacks, vascular

complications, contrast-induced nephropathy and a number of angiographic complications.

Although mortality after percutaneous coronary intervention is rare (less than 1 percent), it is higher in the setting of ST elevation myocardial infarction, cardiogenic shock and in patients who develop an occlusion with poor left ventricular function. Periprocedural myocardial infarction is one of the most common complications of percutaneous coronary intervention. Two classification systems have been used to classify myocardial infarction after percutaneous coronary intervention. The World Health Organization classification system defines myocardial infarction a total creatine phosphokinase isoenzyme (CPK) elevation more than two times normal in association with elevation of the CPK-MB isoform. Using this definition periprocedural myocardial infarction occurs after 1 to 2 percent of percutaneous coronary intervention procedures. The FDA classification system defines myocardial infarction as an elevation in CPK-MB of three times normal or higher after the procedure (Califf, Abdelmeguid, Kuntz, Popma, Davidson, Cohen, Kleiman, Mahaffey, Topol, Pepine, Lipicky, Granger, Harrington, Tardiff, Crenshaw, Bauman, Zuckerman, Chaitman, Bittl and Ohman, 1998).

A number of complications may occur during stenting and depending on their severity and duration, may result in periprocedural myocardial infarction. In coronary dissections that extend deeper into the media or adventitia or begin to compromise the true lumen of the vessel, clinical ischemia may develop. Whereas most intraprocedural dissections can be treated promptly with stenting, significant residual dissections of the treated artery occur in 1.7 percent of patients. These residual dissections raise the risk of post procedure myocardial infarction, need for emergent CABG and stent thrombosis increase mortality threefold (Biondi-Zoccai, Agostoni, Sangiorgi, Airoldi, Cosgrave, Chieffo, Barbagallo, Tamburino, Vittori, Falchetti, Margheri, Briguori, Remigi, Iakovou and Colombo, 2006).

2.2.4.2 Late Clinical Outcome

Clinical restenosis after stent implantation is less common (10 to 20 percent) and is attributable to intimal hyperplasia within the stent. Clinical recurrence caused by restenosis is least common (3 to 5 percent) after drug-eluting stent placement because of focal tissue growth within the stent or at its margins. Another cause of clinical events after percutaneous coronary intervention is the progression of coronary atherosclerosis at a site remote from that treated earlier by percutaneous coronary intervention. Death and myocardial infarction can also result from sudden rupture of a plaque that is remote from the site of the initial intervention. These processes can be partially distinguished by the timing of their occurrence. Clinical restenosis resulting from lumen renarrowing at the site of stenting generally develops within 6 to 9 months after intervention. Whereas death and myocardial infarction due to plaque instability may occur at any point after percutaneous coronary intervention at a low but constant risk (1 to 2 percent per year). Predictors of higher risk of all cause late mortality include advanced age, reduced left ventricular function or congestive heart failure, presence of diabetes mellitus, number of diseased vessels, inoperable disease and severe comorbid conditions. Risk factors for restenosis after coronary stent placement include age, a history of diabetes, a longer lesion or total stent length, small post procedural minimal lumen diameters and left anterior descending lesion location (Baim, Kuntz and Popma, 2008).

2.2.4.3 In-Stent Restenosis

Accumulation of neointimal tissue within the axial stent length accounts for virtually all cases of in-stent restenosis. Recurrence of symptoms may occur in 10 to 20 percent of patients within 12 months after stent implantation; after 6 to 12 months, improvements of the lumen dimensions related to scar retraction have been noted. Although some patients with multivessel CAD or multiple stent restenosis are best served by referral for CABG, the majority of patients with in-stent restenosis can be safely and effectively treated with

repeated percutaneous coronary intervention, with the mechanism of benefit related to both expansion of the stent and extrusion of the tissue through the stent struts and along its length. Early tissue recoil may also occur immediately after percutaneous coronary intervention in those with in-stent restenosis. Recurrence rates after PTCA for stent restenosis ranged from 10 to 20 percent, although higher (up to 80 percent) recurrence rates have been reported depending on vessel size, pattern of restenosis (e.g. intrastent, stent margin, or remote disease) and the time to presentation. “Very late” (>1 year) restenosis occurs rarely after coronary stenting in native coronary arteries (Kimura, Yokoi, Nakagawa, Tamura, Kaburagi, Sawada, Sato, Yokoi, Hamasaki, Nosaka and Nobuyoshi, 1996).

2.2.4.4 Stent Thrombosis

Stent thrombosis is a catastrophic complication of percutaneous coronary intervention and is associated with a mortality of between 25 to 40 percent (Wenaswesar, Daemen, Zwahlen, van Domburg, Juni, Vaina, Hellige, Tsuchida, Morger, Boersma, Kukreja, Meier, Serruys and Windecker, 2008). Various trials report the frequency of stent thrombosis as 0.8-2 percent (Camenzind, Steg and Wijns, 2008). Most evaluations however come from registries that are likely to underestimate the real prevalence (Collet, Hulot and Montalescot, 2009). The timing of the stent thrombosis is defined as acute (<24 hours), subacute (24 hours to 30 days), late (30 days to 1 year), and very late (after 1 year) (Cutlip, 2006). The risk for stent thrombosis is most likely multi-factorial (table 1) and influenced by clinical, anatomic and procedural characteristics (van Werkum, Heestermans, Zomer, Kelder, Suttorp, Rensing, Koolen, Brueren, Dambrink, Verheugt and ten Berg, 2009). From the e-Cypher registry of 15,157 patients, it was determined that age, diabetes, acute coronary syndrome, treatment of chronic total occlusion and multivessel percutaneous coronary intervention were predictors for stent thrombosis (Gershlick, Guagliumi, Guyon, Lotan, Schofer, Seth, Sousa, Lotan, Schofer, Seth, Sousa, Wijns, Berge, Deme, Stoll and Urban, 2006).

Although the overall in incidence of stent thrombosis is rare, it still presents a serious and considerable clinical problem due to high mortality especially in cases of late stent thrombosis with DES.

Table 1: Established risk factors for stent thrombosis

Treatment discontinuation	Stent malpositioning
Active smoking	Poor stent apposition
Diabetes	Recent myocardial infarction
Bifurcations	Cancer
Small arteries	Renal failure
Low TIMI flow	Heart failure
Increased stent length	Chronic inflammatory diseases
Stent type	Polymer type

2.2.5 Delayed Endothelialisation

A prolonged window of vulnerability to thrombosis with DES has been a concern with pre-clinical studies demonstrating delayed healing and endothelialisation (Finn, Kolodgie, Harnek, Guerrero, Acampado, Tefera, Skorija, Weber, Gold and Virmani, 2005). Sirolimus effectively suppress endothelial cell proliferation in vitro (Parry, Brosius, Thyagarajan, Carter, Argentieri, Falotico and Siekierka, 2005). The compound may also exert a local thrombogenic effect via up regulation of monocyte and endothelial cell tissue factor expression (Rozenberg, Jaschko, Greutert, Kurz, Wnendt, Kuttler, Joch, Grünenfelder, Zünd, Tanner, Lüscher and Matter, 2006). A study performed serial angioscopy up to 22 months after implantation of SES (n = 17) or BMS (n = 11). Using neointimal formation as a surrogate for endothelialisation, they found neointimal coverage of stent struts complete in the BMS group by 3–6 months. In the DES group, there was evidence of slow and ongoing neointimal formation even at 2 years (Awata, Kotani, Uematsu, Morozumi, Watanabe, Onishi, Lida, Sera, Nanto, Hori and Nagata,

2007). In an autopsy registry of 23 DES (implanted > 30 days) and 25 BMS, 14 of the 23 DES had evidence of late thrombosis. Overall, DES had more fibrin and less endothelialisation compared to BMS (Virmani et al, 2004).

2.2.6 Antiplatelet Therapy

Percutaneous coronary intervention requires the use of one or more antiplatelet agents combined with some level of thrombin inhibition in order to prevent thrombus formation on the stents used for percutaneous coronary intervention. In patients with coronary stent implantation, antiplatelet therapy using aspirin and a thienopyridine (e.g. plavix) is the current standard strategy to prevent stent thrombosis. After an intensive worldwide debate concerning the safety of DES and consequently concerning the minimal duration of dual antiplatelet therapy there is consensus at present. Taken together, the international guidelines recommend the duration of 6-12 months after DES implantation and 9-12 months after acute coronary syndrome (Grines, Bonow, Casey, Gardner, Lockhart, Moliterno, O' Gara and Whitlow, 2007). However, a growing number of patients appear to require a more individualized antithrombotic regimen. These patients include those with an additional indication for anticoagulation, patients that need unplanned non-cardiac surgery within the time interval at high risk for stent thrombosis or low responders to the treatment with clopidogrel. In these high risk patients, the individual decision making regarding both the intensity and duration of the antithrombotic therapy has to take the individual risk of severe bleeding complications into account.

Aspirin is an irreversible inhibitor of the enzyme cyclooxygenase that blocks the synthesis of thromboxane A2, a vasoconstricting agent that promotes platelet aggregation. Thienopyridine derivatives cause irreversible platelet inhibition related to their effects on the P2Y12 adenosine diphospated receptor that is responsible for activation of the GP IIb/IIIa complex. Because aspirin and thienopyridine derivatives have synergistic mechanisms of action,

their combination may inhibit platelet aggregation to a greater extent than either agent alone (Baim, Kuntz and Popma, 2005).

Data from a large two-institution (Bern, Rotterdam) cohort study including 8146 patients receiving DES showed that angiography-documented late stent thrombosis (>30 days after percutaneous coronary intervention) occurred at a constant rate of 0.6 percent per year for up to 3 years after implantation. Depending on the institution, patients were to have received clopidogrel for at least 3 or 6 months (Rotterdam, depending on type of drug-eluting stent) or for at least 12 months irrespective of drug-eluting stent type (Bern) in addition to aspirin. Although absence of clopidogrel was not a significant predictor of overall or late stent thrombosis in the Rotterdam cohort, it was noted that among patients with late stent thrombosis, 31 (51 percent) received only one antiplatelet drug and 16 (26 percent) were not on antiplatelet therapy; of 31 patients with late thrombosis who were receiving only aspirin, 30 experienced thrombosis after the prescription for clopidogrel had expired *(*Daemen, Wenaweser, Tsuchida, Abrecht, Vaina, Morger, Kukreja, Jüni, Sianos, Hellige, van Domburg, Hess, Boersma, Meier, Windecker and Serruys, 2007). The United States study of more than 4600 patients, carried out by Duke University researchers, found similar results. Patients were followed up at 6, 12, and 24 months for death, non-fatal myocardial infarction or the composite of death/myocardial infarction. Patients with drug eluting stents who stopped taking clopidogrel had more than twice the risk of death or heart attack than those who continued to take the drug. The overall risk over the pursuing 18 months was 7.2 percent versus 3.1 percent. These findings strongly suggest that prolonged antiplatelet therapy may be beneficial with drug-eluting stents (Eisenstein, Anstrom, Kong, Shaw, Tuttle, Mark, Kramer, Harrington, Matchar, Kandzari, Peterson, Schulman and Califf, 2007.).

Patients who undergo non-cardiac surgery early after coronary stenting with interruption of the combined antiplatelet therapy are at increased risk for stent thrombosis and its potentially fatal consequences (Joseph, Kałuza, Lee,

Raizner and Raizner, 2000; Vicenzi, Meislitzer, Heitzinger, Halaj, Fleisher, and Metzler, 2006; Wilson, Fasseas, Orford, Lennon, Horlocker, Charnoff, Melby and Berger, 2003). A metaanalysis of eight observational studies showed that the mortality rate in such patients ranged from 2.5-21.4 percent (Chiche, Hamon, Plaud and Riddell, 2007). Therefore, if possible, one should avoid and delay elective non-cardiac surgery in patients who have had recent coronary stenting (Grines, Bonow, Casey, Gardner, Lockhart, Moliterno, O'Gara and Whitlow, 2007). However, in many patients unexpected diagnoses mandate urgent surgery. These patients need an individualized pre-, peri and post operative management that weighs up the risk of perioperative bleeding versus the risk of stent thrombosis.

2.2.7 The Cypher® Stent

Cordis Corporation developed and manufactured the Cypher® stent. Cypher® stents are specifically designed to reduce in-stent stenosis (Table 2). 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 biostable polymer into the artery wall around the stent to help limit the normal overgrowth of tissue as the healing process takes place. Eighty percent 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 G, by a physiological mechanism (Duisburg and Wessely, 2008). The Cypher® stent received Conformite European Mark approval in Europe in April 2002 and approval by the United States Food and Drug Administration in the United States in May 2003.

Table 2: Detailed information on the Cypher® stent

Stent Geometry	Closed-cell FLEXSEGMENT™ Technology
Material	316L Stainless Steel
Strut Thickness	0.0055"
Crimped Profile	0.044"
Available Sizes (mm)	Diameters: 2.25, 2.50, 2.75, 3.00, 3.50 Lengths: 8, 13, 18, 23, 28, 33
Drug Delivered	Sirolimus (Rapamycin, Rapamune)
Mechanism of Action	Inhibits m TOR to block growth factor induce proliferation. Cytostatic (blocks cell cycle in late G_1phase)
Drug Delivery Vehicle	Controlled-release, nonresorbable, elastomeric polymer coating
Drug Release Kinetics	80% of sirolimus released in 30 days
Approval Status	Approved by FDA

CHAPTER THREE

MATERIALS AND METHODS

The aim of the study was to assess overall safety of sirolimus-eluting coronary stents. The primary objective determines if the antirestenosis efficacy is maintained and the time of development of ischemic events after stenting. The secondary objectives addressed concerns about major adverse cardiac events. The study also tracked patient outcomes with dual anti-platelet therapy. All patients were recruited at the time of the coronary intervention and follow up data was collected one month after index procedure. Thereafter clinical information was collected at six months, twelve months and twenty four months.

3.1 ETHICAL APPROVAL AND CONSENT

Before commencement of the actual investigation, ethical approval was obtained from the Durban University of Technology Ethical Committee. In order to facilitate the study, approval was obtained from the hospital management at Entabeni Hospital. All patients provided written informed consent before enrolment.

3.2 STUDY POPULATION

Dr David Gillmer is an interventional cardiologist who offers private practice cardiology serivces in Durban. The mission of Dr. Gillmer is to provide patients with the best quality and comprehensive cardiovascular care by utilizing the finest clinical expertise and experience supplemented by state-of-the-art equipment, current procedures and pharmacology and incorporating education and life-style changes to enhance the patient's well-being while maintaining a compassionate and caring relationship with the patient and family. The full service non-invasive cardiology procedures includes, complete cardiovascular medical exam, electrocardiograms and treadmill

testing. We also provide invasive cardiology services which include, cardiac catheterization, pacemaker implantation, coronary angiography, carotid and peripheral angiography, balloon angioplasty and stent placement.

3.3 STUDY DESIGN

The study is a descriptive prospective cohort of patients who have received a sirolimus-eluting stent designed to determine the incidence of clinically significant restenosis and major adverse cardiac events. A sample size of thirty patients was recruited from Entabeni Hospital (private hospital), namely Dr D.J. Gillmer's practice January 2008 to June 2008. This hospital was selected as the interventional cardiologist practiced there and the investigator was currently employed as a clinical technologist. The reason for selecting thirty patients is due to the small number of patients receiving a sirolimus-eluting stent as a treatment strategy i.e. approximately six sirolimus-eluting stents are implanted in a month. Allowances had to be made for those patients refusing to participate in the study and patients not meeting the selection criteria.

3.4 SELECTION CRITERIA

3.4.1 Inclusion criteria

- Patients implanted with a sirolimus-eluting stent.
- Patients residing in South Africa.

3.4.2 Exclusion criteria

- Patients had non-cardiac coexisting conditions that resulted in a life expectancy of less than one year.
- Patients participating in another drug or coronary device study.

3.5 THE RECRUITMENT PROCESS

- All patients receiving a sirolimus-eluting stent were potential participants for the study. Patients were sent to critical care unit post procedure and were under the consultant care of Dr D.J Gillmer.
- Here, the principal investigator provided a letter of information to the patient and discussed the purpose and requirements of the study (Appendix 1). Patients were informed that their right to participate in the study was entirely voluntary and that they were entitled to withdraw at any point without affecting the medical treatment rendered to them. They were also informed that all information used in the study would remain confidential and that any data reported in scientific journals or published would not include information identifying them as a patient in the study.
- Once the informed consent was signed, patient data was collected during. Demographic data of patients and cardiac history were collected from review of the doctor's notes and the patient's chart (Apendix 2). Baseline measurements of the patient's vitals during the coronary angiogram were obtained from the clinical technologist. Angiographic features and procedural data were obtained from the radiographer (Appendix 3). Left ventricular ejection fraction, type or location of lesion, reference vessel diameter, lesion length and maximal balloon pressure were variables included in the list. In addition, a specific reason for stenting and the number of stents implanted was included.

3.6 FOLLOW UP

Clinical follow-up was made by personal interview or telephone contact. A detailed questionarre was filled by the principal investigator at 1, 6, 12 and 24 months after discharge (Appendix 4). Patients were followed-up to monitor the possible interim development of angina and major adverse cardiac events (Appendix 5). Major adverse cardiac events included death, myocardial infarction, stent thrombosis and repeat revascularizations. All deaths, regardless of cause, were included. The diagnosis of myocardial

infarction was based on the universal definition of myocardial infarction (Alpert, Thygesen and White, 2007). Stent thrombosis was defined as the definite occurrence of a thrombotic event according to the Academic Research Consortium classification (Cutlip, Windecker, Mehran, Boam, Cohen, van Es, Steg, Morel, Mauri, Vranckx, McFadden, Lansky, Hamon, Krucoff and Serruys, 2007). 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) (Cutlip, 2006). Target vessel revascularization was defined as either percutaneous intervention or surgical revascularization of the stented epicardial vessel. In hospital events were included in the analysis of follow-up events. To ensure accurate assessment of compliance with the study medication regimen, patients were asked whether they were taking aspirin and plavix and how long had they been taking them. If any antiplatelet medication had been discontinued, an attempt was made to determine the specific timing of this action. Duration of antiplatelet therapy was left to the discretion of the cardiologist.

3.7 LIMITATIONS

There were several important limitations of the study. The sample size was small. The study was limited to one interventional cardiologist's practice. The study only used Cypher® sirolimus-eluting stents.

3.8 STATISTICAL ANALYSIS

In evaluating the overall safety of DES, it is important to appraise their net clinical benefit, which can be summarized after considering the stent's beneficial and adverse effects. In the study the benefits of DES relate to recurring symptoms, while adverse effects relate to the increase death, myocardial infarction, stent thrombosis and target lesion revascularization. All data obtained from the questionnaires were depicted on spreadsheets. Descriptive statistics were presented presented as number and percentages.

Statistical analysis was performed with SPSS software (SPSS Inc, Chicago, III, USA, version 6.0). Bar charts were constructed to present findings of the study as a visual summary of results obtained from the data.

CHAPTER FOUR

RESULTS

4.1. CHARACTERISTICS OF THE SAMPLE

The study reports on clinical data from 30 patients, in who the Cypher® Stent was implanted. A total of 32 patients met the study inclusion criteria. Two patients refused to participate in the study. There were differences in age, race and the prevalence of selected cardiovascular diseases.

4.1.1 Age

Their mean age of the studied group was 62.33 years with a standard deviation of 10.99 years and a range from 31 to 75 years. A breakdown of the different age group ranges is illustrated in table 3. There is a reasonably spread of subjects across the arbitrarily assigned age group ranges of 31-45, 46-55, 56-65, 66-75.

4.1.2 Gender

This study consisted of 83 percent males and 17 percent female.

4.1.3 Race

There was a clear preponderance of white subjects [n=25, 83 percent] in keeping with the doctor's normal patient profile, the remainder being made up of coloured and Indian subjects. The complete racial composition of the study group is outlined in table 3.

Table 3: Race and age groups

RACE	MALE	FEMALE	TOTAL
WHITE	21	4	25 (83%)
COLOURED	2	1	3 (10%)
INDIAN	2	0	2 (7%)
AGE RANGE	**MALE**	**FEMALE**	**TOTAL**
31—45	2	0	2
46-55	5	0	5
56-65	8	1	9
66-75	10	4	14

4.1.4 Baseline Characteristics

The baseline characteristics of the study population are shown in table 4. Fifty three percent of patients were being treated for hypertension and approximately six percent had diabetes mellitus. Thirteen percent had a history of myocardial infarction. Seventeen percent of the population had revascularization to coronary arteries prior to enrolment in the study. Seven percent of the study population had coronary artery bypass surgery and ten percent had percutanous transluminal coronary angioplasty or stenting.

Table 4: Baseline characteristics of the study group

VARIABLE	PERCENT
Hypertension	53
Treatment of diabetes mellitus	6
Dietary therapy alone	3
Oral hypoglycemic agent	3
Insulin	0
Prior myocardial infarction	13
Prior percutaneous revascularization	10
Prior coronary bypass surgery	7

4.2 ANGIOGRAPHIC CHARACTERISTICS

Baseline patient monitoring parameters were taken for all patients. Heart rate (HR), aortic pressure (AO) and left ventricular ejection fraction (LVEF) are shown in table 5.

Table 5: Baseline readings of monitored parameters

	HR	SYSTOLIC PRESSURE	DIASTOLIC PRESSURE	LVEF
N Valid	30	30	30	30
Missing	0	0	0	13
Mean	72.2	146.63	78.87	55
Std.	13.41	29	10.44	15.29
Deviation	45	100	60	29
Minimum	98	236	109	80
Maximum				

The angiographic characteristics of the study group are shown in table 6. Most patients (63 percent) presented with multivessel coronary disease. Thirty percent of the population had two-vessel disease. The left anterior descending artery was the most common target for intervention [n=34, 53 percent].Thirty three percent of the population had triple-vessel disease. Nine percent of the population had lesions in a ramus and three percent in a saphenous vein graft.

Table 6: Angiographic characteristics of the study group

AFFECTED CORONARY VESSEL	PERCENT
LAD	53
CX	15
RCA	20
DIAG	0
RAMUS	9
OM	0
GRAFT	3
PDA	0
VESSEL SITE	
Proximal	35
Middle	53
Distal	12
SEVERITY OF CAD	
Single-vessel disease	37
Two-vessel disease	30
Three-vessel disease	33

4.3 PROCEDURAL CHARACTERISTICS

Thirty percent of the patients had been hospitalized with acute myocardial infarction at the time of their coronary stent implantation. Sixty percent of the population presented with angina (figure 6). Three percent of patients had silent ischemia.

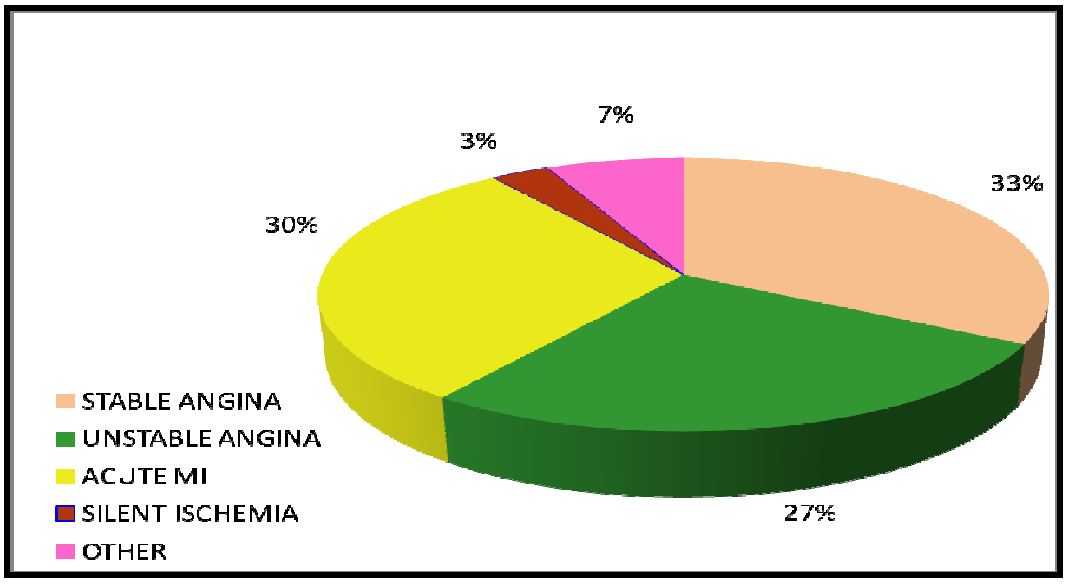

Figure 6: Indications for percutaneous coronary intervention

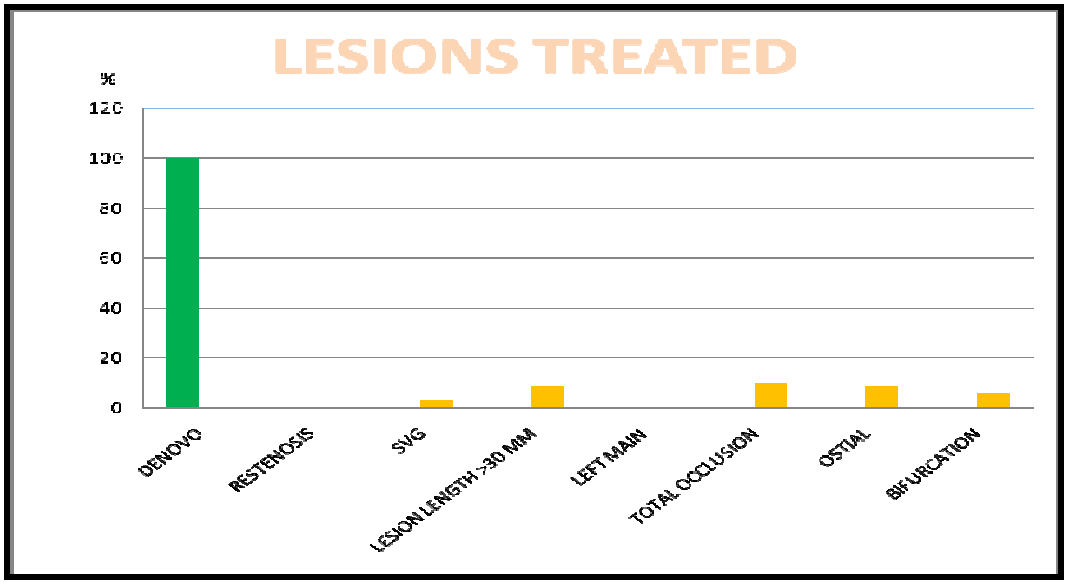

Figure 7: Lesions treated

All the lesions were denovo as shown in figure 7. On and off-label usage is shown in table 7. Forty percent of patients had stents implanted according to Food and Drug Administration approved indications. It has been estimated that sixty percent of sirolimus-eluting stents use in the study has been “off label”, i.e. used in patients with clinical conditions that donot precisely fit the Food and Drug Administration approved clinical criteria. Forty percent of the population had single off-label indications and the remaining twenty percent had multiple off-label indications.

Table 7: On and Off-label Use

INDICATION	PERCENT
On-label use	40
Off-label use	60
Bifurcation lesion	7
Ostial lesion	0
Chronic total occlusion	10
BMS restenosis	0
Left main coronary artery	0
Saphenous vein graft lesion	3
LVEF < 30 percent	7
Acute myocardial infarction	30
Internal mammary artery graft lesion	0
Stented length > 30mm	23
Stent diameter <2.5mm or >3.75mm	10
PCI of > 1 lesion	13
Single off-label indication	40
Multiple off-label indication	20

A total of thirty four coronary lesions were treated. Thirty five stents were used as one lesion required overlapping stents. Overall, the average lesion

length was 22.32 ± 6.63mm and the average reference vessel diameter was 2.77 ± 0.41mm (table 8). The varying stent lengths and diameters used are shown in figure 8 and 9. Procedural success was high with no major in hospital complications. Approximately thirteen percent of the patients had stents implanted in two diseased vessels. Approximately three percent of the patients had a single stent implanted in the proximal and distal segment of an artery.

Table 8: Procedural characteristics of the study group

Number of lesions/patient	1.93 ± 0.87
Number of SES/patient	1.17 ± 0.38
Number of SES/lesion	0.60 ± 0.27
Direct stenting (%)	38
Postdilation (%)	26
Predilation (%)	41
Pressure deployment (atm)	15.48 ± 3.80
Stent length (mm)	23.08 ± 6.56
Stent diameter (mm)	2.93 ± 0.42
Lesion length (on site visual estimate, mm)	22.32 ± 6.63
Reference vessel diameter (on site visual estimate, mm)	2.77 ± 0.41
Clinical success (%)	100
Procedural success (%)	100

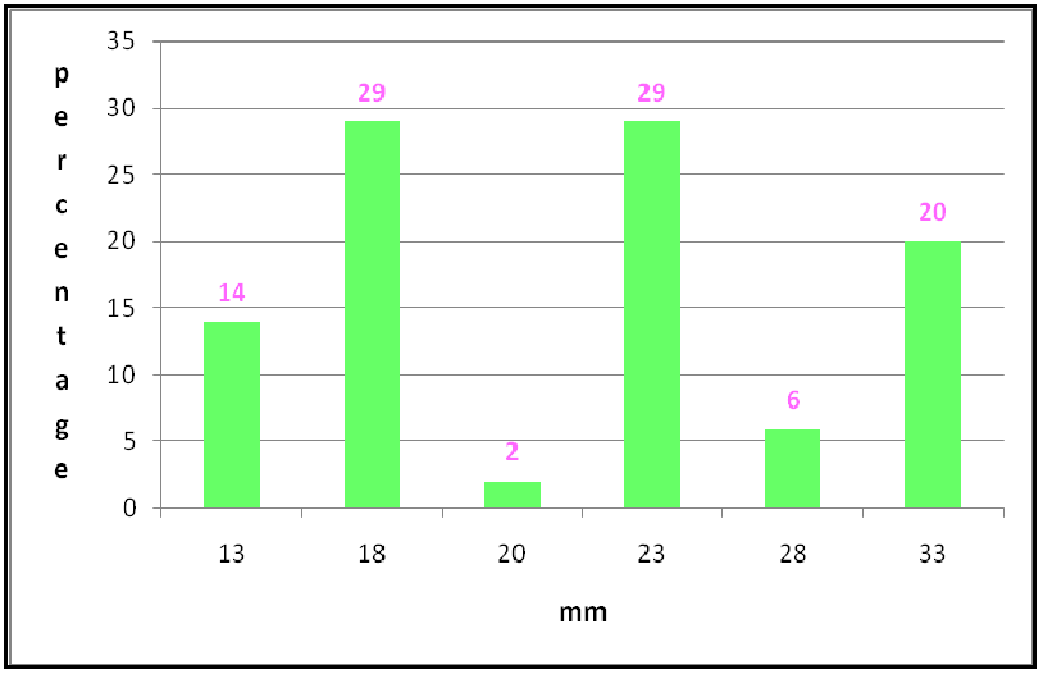

Figure 8: Sirolimus-eluting stent lengths used

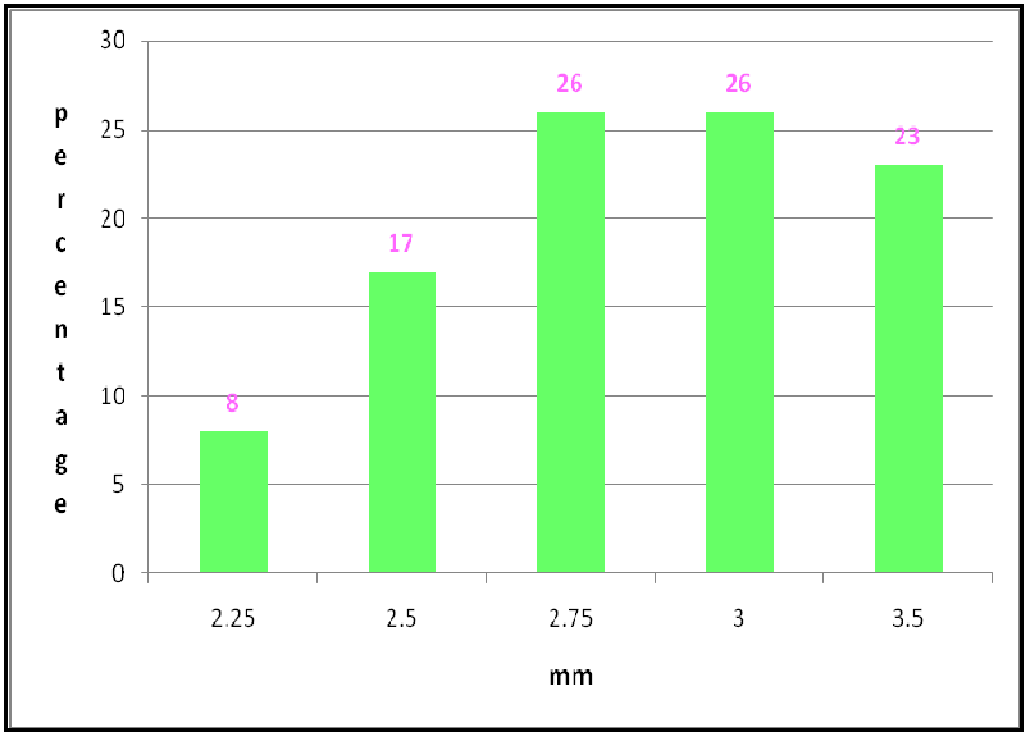

Figure 9: Sirolimus-eluting stent diameters used

4.4. Clinical Outcomes

Complete compliance for all two year follow-up end points was accomplished for 30 patients. There were no recurring symptoms of angina as shown in figure 10. There were no incidences of death, myocardial infarction, target lesion revascularization and stent thrombosis as shown by the survival curves in figure 12. At six month follow up, there was one incidence of a bleeding complication. Overall, 6% of those receiving a drug-eluting stent required a repeat angiogram by year 2 of follow-up. Figure 11 shows low frequency of adverse events for all clinical outcomes. Nineteen percent of the population experienced adverse events that were not related to the sirolimus-eluting stenting procedure. Timing of randomization and adherence to the study treatment during follow-up period is shown in figure 13. All patients were started on a course of dual antiplatelet therapy. Aspirin was maintained over the two years. There was a gradual decrease in the number of patients taking plavix over the study period. At 24 months none of the patients were on plavix.

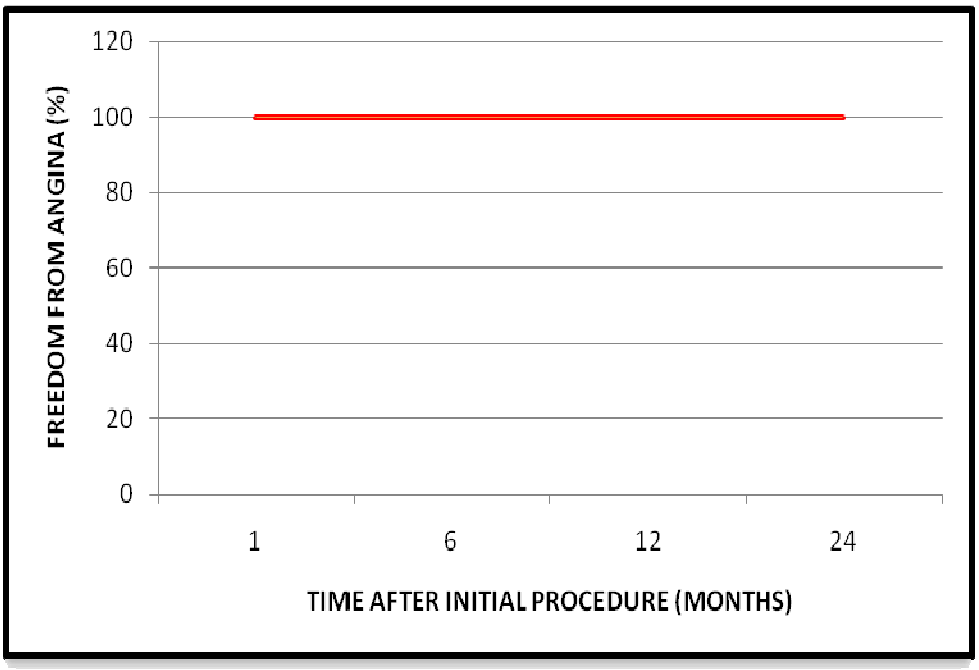

Figure 10: Angina status of patients

Sample-Size Determination
Parameter to be estimated: normal mean
Sample size: 30
Confidence level: 95.0%
Sigma: 1.0 (to be estimated)

The tolerance will be +- 0.373407

The StatAdvisor
This procedure determines the sample size required when estimating the mean of a normal distribution. Assuming that the standard deviation of the normal distribution equals 1.0, 30 observations will estimate the true mu to within +/-0.373407 with 95.0% confidence.

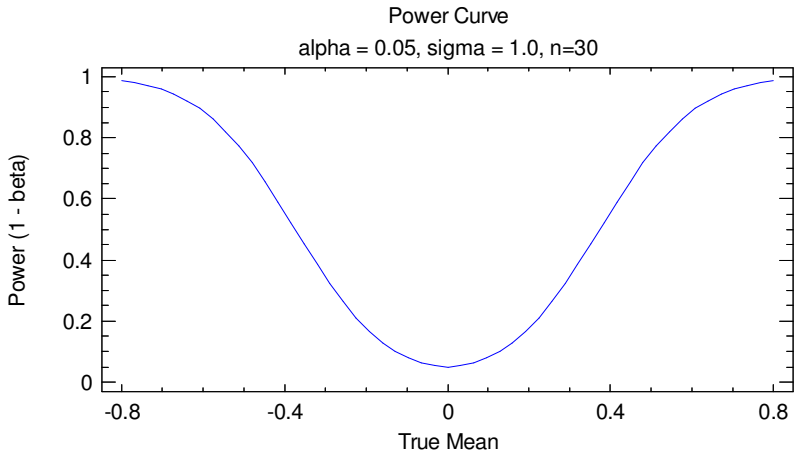

Figure 11: Tolerance

Using stat graphics statiscal software the sample size of 30 had tolerance of 0.37.

ONE MONTH

EVENTS	PERCENTAGE
SES device failure	0
Procedural complications	0
Bleeding	0
Cardiovascular events	0
Cerebroscular events	0
Other adverse events	10
Coronary angiography	3

SIX MONTHS

EVENTS	PERCENTAGE
SES device failure	0
Procedural complications	0
Bleeding	3
Cardiovascular events	0
Cerebroscular events	0
Other adverse events	3
Coronary angiography	3

TWELVE MONTHS

EVENTS	PERCENTAGE
SES device failure	0
Procedural complications	0
Bleeding	0
Cardiovascular events	0
Cerebroscular events	0
Other adverse events	3
Coronary angiography	0

TWENTY FOUR MONTHS

EVENTS	PERCENTAGE
SES device failure	0
Procedural complications	0
Bleeding	0
Cardiovascular events	0
Cerebroscular events	0
Other adverse events	3
Coronary angiography	0

Figure 12: Events reported at follow-up

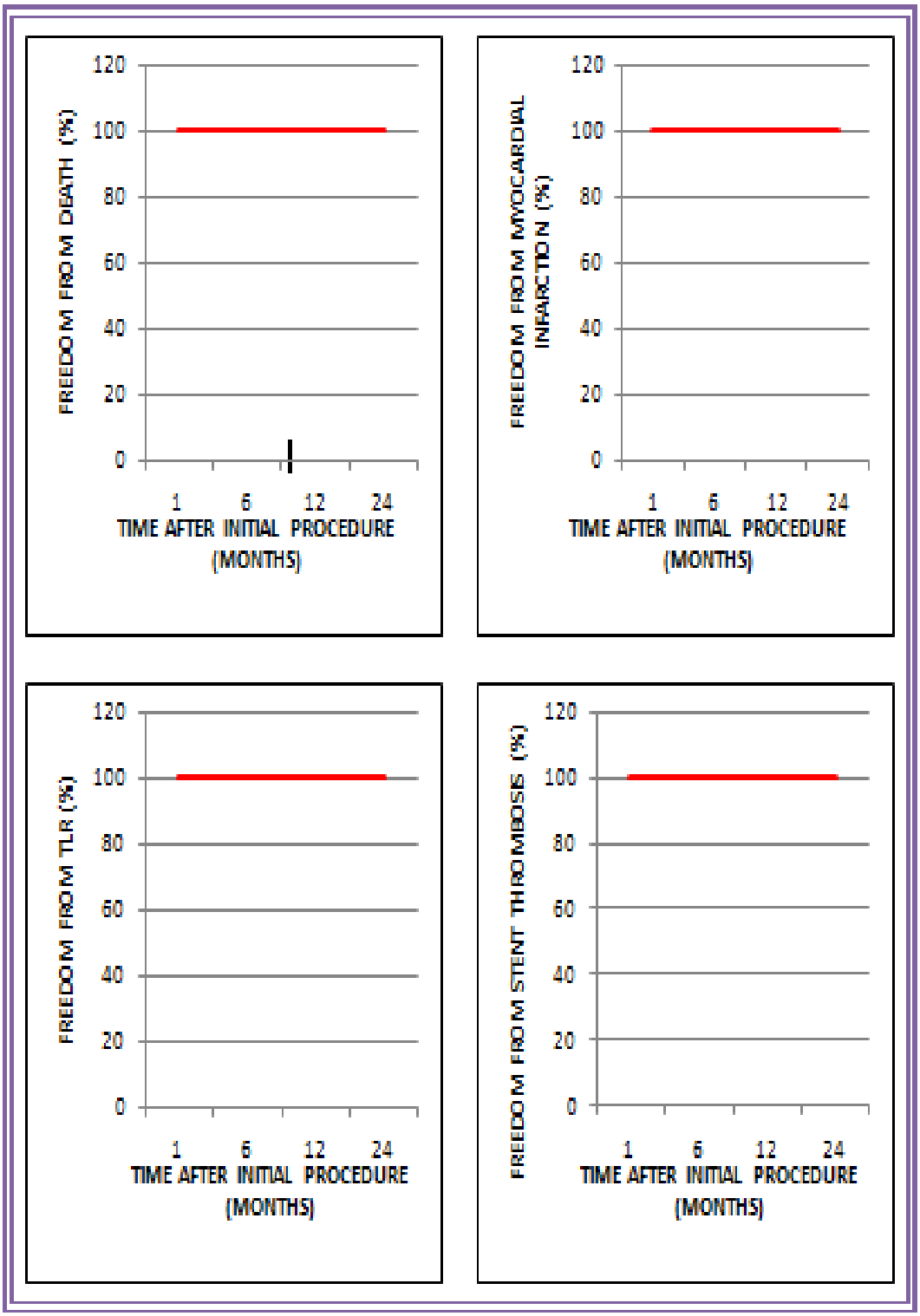

Figure 13: Survival curves of major adverse cardiac events

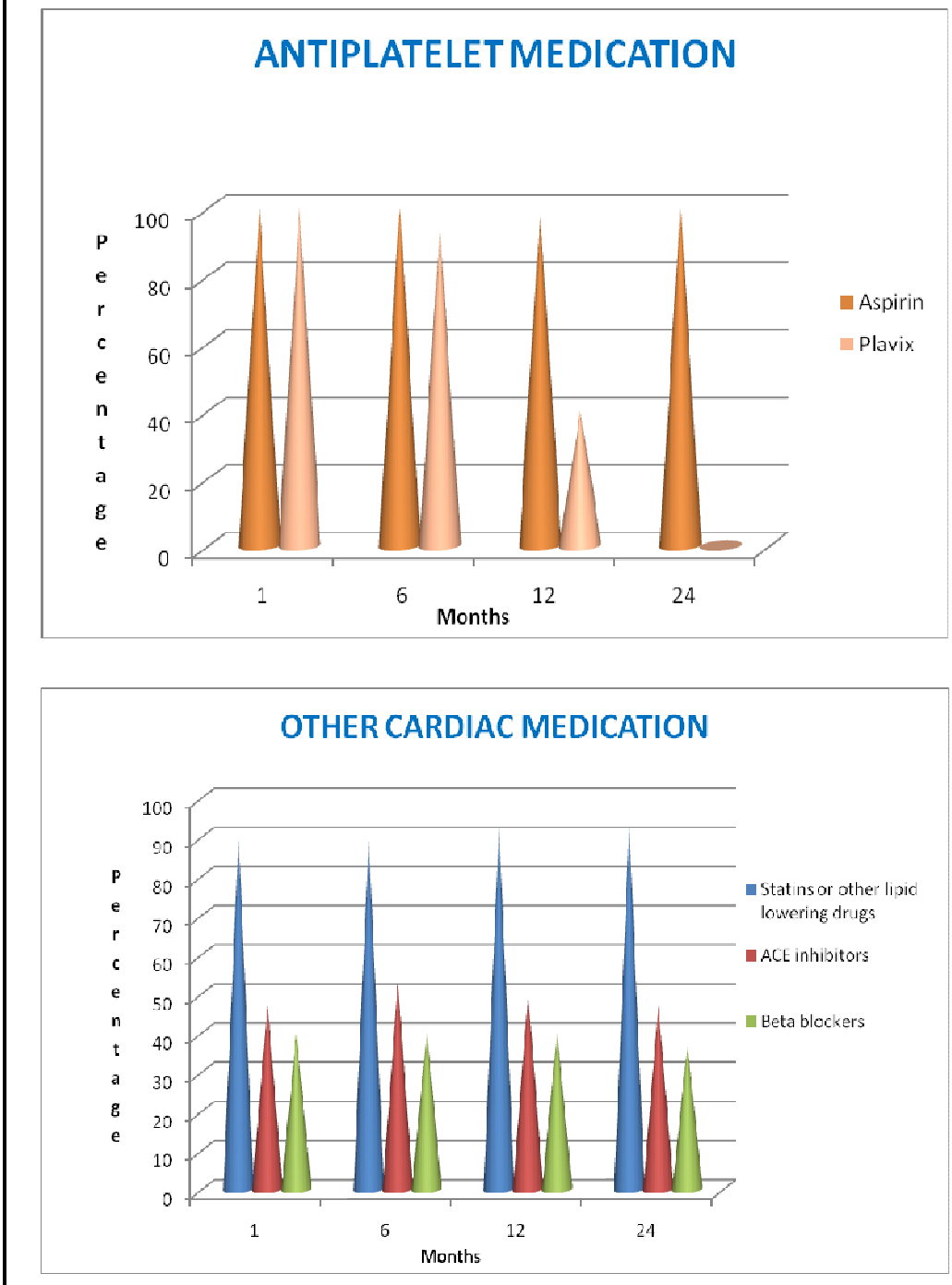

Figure 14: Medications at time of follow up

CHAPTER FIVE

DISCUSSION

Since the introduction of DES, there has been an evolving change in the treatment paradigm such that the vast majority of current patients receive sirolimus-eluting stents during percutaneous coronary interventions. The study was a prospective study designed to evaluate the outcomes of percutaneous coronary intervention with a sirolimus-eluting stent at our medical practice out to two years. The main impetus for pursuing a two year follow-up was to assess overall safety of sirolimus-eluting coronary stents. The primary objective determines if the antirestenosis efficacy is maintained and the time of development of ischemic events after stenting. The secondary objectives addressed concerns about major adverse cardiac events. This study also tracked patient outcomes with dual anti-platelet therapy.

In evaluating the overall safety of DES, it is important to appraise their net clinical benefit, which can be summarized after considering the stent's beneficial and adverse effects. It is clear that the benefits of DES relate to recurring symptoms, while adverse effects relate to the increase death, myocardial infarction, stent thrombosis and target lesion revascularization (TLR). At two years, the study demonstrated the following positive results for sirolimus-eluting stents:

- All patients remained angina free.
- No major adverse cardiac events.
- One bleeding event documented.
- Two patients had angiograms

Our study shows that sirolimus-eluting stents were effective in treating coronary artery disease as there was no recurrence of angina. Complete follow-up data for all patients to the end of years two allowed us to estimate

all event rates precisely at 1 month, 6 months, 12 months and 24 months. There were no in stent restenosis indicating that the clinical benefit conferred by sirolimus-eluting stents is sustained at two years. Thus, it is unlikely that coronary stenting simply delays clinical restenosis instead of preventing it. Major adverse cardiac events, is an important composite clinical measure of safety and efficacy outcomes for patients. Figure 10 shows that there were no protocol-defined major adverse cardiac events. Two patients had angiograms during the follow up period. The results showed patent stents with no new narrowings. At four months after the index procedure, one patient complained of not feeling well and was looking pale. At peak exercise on the treadmill, the patient had short runs of ventricular tachycardia. An angiogram was performed showing effectively normal coronary arteries. The patient was discharged and prescribed with new medication. Another patient presented with peripheral vascular disease and the cardiologist decided on stenting the left common iliac artery. Since the patient was in the catheterization laboratory, the cardiologist decided to perform a coronary angiogram. The fairly low overall clinical outcomes (figure 11) suggest that the risk–benefit equation for overall safety favors sirolimus-eluting stents. Nineteen percent of the study population had adverse events. The events reported were not related to the sirolimus stent or the implantation procedure.

An observational analysis from the Basel Stent Cost-Effectiveness Trial-Late Thrombotic Events (Bader et al, 2006), 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 (Eisenstein et al, 2007) and in a diabetic population (Brar, Kim, Brar, Zadegan, Ree, Liu, Mansukhani, Aharonian, Hyett and Shen, 2008). A Dutch registry of 437 patients with stent thrombosis found a strong correlation between late stent thrombosis and discontinuing clopidogrel at 6 months (van Werkum, Heestermans, Zomer, Kelder, Suttorp, Rensing, Koolen, Brueren,

Dambrink, Verheugt and ten Berg, 2009). This registry also reported high rates of death, myocardial infarction, and recurrent stent thrombosis, with poor outcomes occurring more frequently in patients with low ejection fraction, diabetes, complex lesions, long stent length, TIMI flow grade <3, and implantation of additional stents for treatment of the stent thrombosis (van Werkum, Heestermans, Zomer, Kelder, Suttorp, Rensing, Koolen, Brueren, Dambrink, Verheugt and ten Berg, 2009). 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. Aspirin greater than or equal to 81 mg daily was prescribed indefinitely and plavix 75 mg/day was prescribed. Patients also received standard pharmacologic therapy (e.g. statins, beta-blockers or angiotensin-converting-enzyme (ACE) inhibitors as appropriate, at the discretion of the responsible doctor. The duration of the combined antiplatelet therapy is demonstrated in figure 13. Plavix treatment varied from a minimum of four weeks to a maximum duration of 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. 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. According to the treatment strategy, sixty percent of patients were started on a six month course of dual antiplatelet therapy and forty percent on a twelve month course. The entire forty percent of the patients adhered to the prescribed plavix therapy out to one year. Overall, fifty three percent of patients on the six month course completed the full duration. One patient underwent a non-cardiac invasive procedure during the study. The doctor decided to discontinue plavix treatment early. Another patient was hospitalized and major bleeding was observed in the fourth month after stent implantation. Plavix was stopped immediately the patient was treated successfully.

One patient, within the first month after stent implantation needed a thorascopy that urged intentional interruption in the dual-antiplatelet therapy. Current percutaneous coronary intervention guidelines recommend that clopidogrel administration be continued ideally up to twelve months after implantation of DES in patients who are not at high risk for bleeding (King, Smith, Hirshfeld, Jacobs, Morrison and Williams, 2008). If confirmed in additional studies, these results would suggest that dual antiplatelet therapy with aspirin and clopidogrel from 6 months to one year is adequate.

Given that our patients tend to have high-risk profiles, our results correspond with those of previous randomized studies in which relatively high-risk patients showed better clinical outcomes after sirolimus-eluting stent use (Windecker, Remondino, Eberli, Jüni, Räber, Wenaweser, Togni, Billinger, Tüller, Seiler, Roffi, Corti, Sütsch, Maier, Lüscher, Hess, Egger and Meier, 2005; Kastrati, Dibra, Eberle, Mehilli, Suarez de Lezo, Goy, Ulm and Schömig, 2005; Ellis et al, 2007). The patient and lesion types studied include patients with diabetes (6 percent of patients; 2 patients), patients with multi-vessel disease (63 percent of patients; 19 patients), patients with longer lesions (>30 mm; 23 percent of lesions; 7 patients) and patients with smaller vessels (reference vessel diameter < 2.5 mm, 8 percent of lesions, 3 patients). Patients who received DES were old and more likely to be hypertensive. Their index intervention was less likely to be emergent.

We observed that more than half of all use of sirolimus-eluting stenting occured in off-label settings as shown in table 7. In keeping with the exclusion criteria from the pivotal trials, off-label indications were defined as acute myocardial infarction, left ventricular dysfunction less than 30 percent, stented length greater than 30 mm, stent diameter less than 2.5mm or greater than 3.75mm, percutaneous coronary intervention of more than one lesion, and intervention to the left main coronary artery, bypass graft, chronic total occlusion, restenosis, or bifurcation lesion (Austin, Eteiba, Flapan, Jennings, McConnachie, Northcote, Oldroyd, Pell, Pell, Slack and Starkey,

2008). 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 (Baim, Kuntz and Popma, 2008). All procedures were performed by the cardiologist according to current guidelines of interventional procedures. In the present study, one patient (3 percent) had a Cypher® Select sirolimus-eluting stent implanted in a seven year old saphenous vein graft. Ten percent of patients had lesions that were chronic total occlusions.

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 (Beohar, Davidson, Kip, Goodreaum, Vlachos, Meyers, Benzuly, Flaherty, Ricciardi, Bennett and Williams, 2007; Win, Caldera, Maresh, Lopez, Rihal, Parikh, Granada, Marulkar, Nassif, Cohen and Kleiman, 2007). In 2007, a convened Food and Drug Administration (FDA) circulatory system devices advisory panel 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 (Shuchman, 2007). The 5-year results from RAVEL, SIRIUS, and TAXUS VI, all reaffirm the long-term reduction in target lesion revascularisation with DES. These benefits have also been consistently reproduced in registries, randomized studies and meta-analyses of patients treated for 'off-label' indications (Ko, Chiu, Guo, Austin, Goeree, Cohen, Labinaz and Tu, 2009; Chieffo, Colombo and Latib, 2008; Carlsson, James, Lindbäck, Scherstén, Nilsson, Stenestrand and Lagerqvist, 2009). The two-year results from our study indicate that in spite of the overall patient and lesion complexity, sirolimus-eluting stent exhibits positive results.

Our study was entirely funded from public sources, without any involvement from industry. There were several important limitations in our study. It was observational in nature. The number of patients and the duration of the study were limited. Our study was not a randomized clinical trial, and there may still be unmeasured confounding factors that contribute to our findings. For these reasons, these findings cannot be generalized to the broader community based on this study alone. The safety of drug-eluting stents in our study warrants further investigation and should be confirmed or refuted through large, randomized clinical trials with longer-term follow-up.

CHAPTER SIX

CONCLUSION

On the basis of the clinical results of this 24-month study, one might reasonably conclude that treatment of lesions with sirolimus-eluting stents is safe and effective. Our study evaluated CYPHER® Stent sirolimus-eluting stent in a diverse population of patients and lesion types, including diabetics, patients with multi-vessel disease and patients with highly complex lesions. Our findings indicate that off-label use of DES is common at our medical practice. However, even with off-label use of DES, all absolute event rates following coronary stenting remain relatively low. This should provide some confidence that late untoward events are unlikely to be associated with sirolimus-eluting stents. Higher initial procedural costs for drug-eluting stents seem to be compensated by lower costs during follow-up. The study reinforces the belief in the strong clinical performance of the sirolimus-eluting stent across a broad range of patients. The positive outcomes seen in this study add to the clinical evidence supporting the sirolimus-eluting stent. If the outcome for these stents persists, drug-eluting stents will unquestionably become the standard of use.

FUTURE WORK

As a consequence, in recent years, the focus of clinical research has been on the development of novel drug carrier systems including absorbable (or biodegradable) polymers and nonpolymeric stent surfaces. One such stent is the BioMatrix stent of Biosensors International, which has been approved by European authorities in January 2008. The Nevo stent of Cordis/Johnson and Johnson also uses a biodegradable coating and is currently undergoing trials. While available safety data for the next-generation DES appears promising, guarded optimism is warranted while larger patient numbers and longer follow-up periods accrue (Abizaid and Costa, 2010).

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APPENDIX 1a

Department of Biomedical and Clinical Technology

Faculty of Health Sciences

P O Box 1334, Durban, 4000

LETTER OF INFORMATION AND CONSENT

TITLE OF THE RESEARCH STUDY:

The assessment of two year clinical outcomes after stent implantation for the treatment of coronary artery disease.

PRINCIPAL INVESTIGATOR:

Miss A Harrypaul, student in Masters Degree in Clinical Technology at the Durban University of Technology.

BRIEF INTRODUCTION:

You are asked to consent to the access and the use of certain personal data with respect to the safety and/or efficacy of the following medical device: Cypher® Select sirolimus-eluting coronary stent. Before you consent to grant access to your personal data for the study, please read the following.

OUTLINE OF THE PROCEDURES:

You underwent a stent procedure and the Cypher® Select sirolimus-eluting coronary stent(s) was/were placed into a coronary artery in order to provide a wider opening for better blood flow. You are being invited to allow access to and use of your personal data related to this above mentioned procedure as

well as to provide information about your cardiac health at specific intervals (1, 6, 12, and 24 months) since this procedure.

PURPOSE:

Data from approximately 30 patients will be collected and analyzed. The information obtained from this study may be used to improve future treatment that will be offered to other patients suffering from the same disease.

VOLUNTARY PARTICIPATION/WITHDRAWAL

You have the right to choose not to participate as you also have the right to withdraw your participation at any time. If you withdraw from this study, the medical information (data) that has been collected prior to your decision to withdraw will not be discarded, and will be used in the analysis, unless you specifically request for the data not to be used. Any questions that you may have will be answered by the researcher at any stage of the study.

REMUNERATION:

Your decision whether to provide access to your data as well as to provide additional information about your cardiac health is completely up to you and voluntary. You will not receive any compensation if you decide to provide access to your data, nor will you experience any disadvantage if you deny.

CONFIDENTIALITY:

All information concerning you will be kept private and confidential. Should there be need to publish any information, it will be in a way that you cannot be identified.

RESEARCH-RELATED INJURY:

There will not be any research related injuries.

PERSONS TO CONTACT IN THE EVENT OF ANY PROBLEMS OR QUERIES:

Miss A Harrypaul	Dr J.K Adam	Dr R.B. Dyer
Principal Investigator	Supervisor	Supervisor
031 2099168	031 373 5291	031 2615031

STATEMENT OF AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

I,……subject's full name, ID number……., have read this document in its entirety and understand its contents. Where I have had any questions or queries, these have been explained to me by……..to my satisfaction. Furthermore, I fully understand that I may withdraw from this study at any stage without any adverse consequences and my future health care will not be compromised. I, therefore, voluntarily agree to participate in this study.

Subject's name ……..…….….. **Subject's signature**…….…
Date:……..……

Researcher's name ……..…... **Researcher's signature**……..……
Date:……..……

Witness name ……..……. **Witness signature**……..……
Date:……..……

Supervisor's name……..... **Supervisors signature**……
Date:……..……

APPENDIX 1b

Department of Biomedical and Clinical Technology

Faculty of Health Sciences

P O Box 1334, Durban, 4000

ISIVUMELWANO SOKUNGENELA UCWANINGO/IMFOMU LOKUZIVUMELA

ISIHLOKA SOCWANINGO:

Ukunhlolwa Kwemiphumela yeminyalsa emibilo emuve kokufakwa kwe stenti ukulapha isifo senhliziyo-coronary (imithambo) artery disease.

IGAMA IOMFUNDI OCWANINGOAYO:

Miss A Harrypaul

ISINGENISO:

Uyacelwa ukuba unikeze imvume ukthi kusetshenziswe imininingwane yakho mayelona nokuphepha nokwethembeka kwolomshini yokwelapha: Cypher® Select sirolimus-eluting coronary stent. Ngaphabi kokuvuma ukunikela ngolwazi ngminingwane yakho ngaloluncwaningo uyacelwa ukuthi ufunde lokhu okulondelayo.

INQUBO:

Wenziwe uqhaqho kwabekwa i-Cypher® Select sirolimus-eluting coronary stent(s) yabekwa emthanjeni ohambisa igazi enhliziyweni ukwenzela ulcuvula imithambo kakhuellwena ukuze igazi lihambe kalula uyamenywa

ulcuba uvulele futhi kusetshenziswe imininingwane yabho ephathelene nalenqubo engenhla futhi unikezele nangemininingwane ngempilo yenhliziyo yakho ngalezi zikhawu zezingyanga-1, 6, 12 no 24 weeinyanga kusukela wenzilwa lolu qhagho.

INHLOSO YALDLUCWANINGO:

Kuzoqoqwa ulwazi ezingulwini ezilinganiselwa ku 30 bese kuyacutshungulwa. Ulwazi oluyothalakala kulolu ncwaningo kungenzenka lusetshenziswe ukwenza ncono usizo ezinye izinguli eziyobe ziguliswa yisifo esifonayo. Isiqumo ekunikezelweni ngolwazi lwemininingwane yakho kanjalo nolwazi ngesimo senhlieiyo yakho kusekuthandeni kwakho nagomusa wakho. Akukho sinxephezulo oysithola mawuquma ukunikezela nge miningwane yakho futhi ngeke uhlangabezane nokunswaswa uma wenqabu.

KUYIMFIHLO

Lonke ulwazi oluzotholakala ubuzwa luzoba imfihlo. Ulwazi oluyoqokelelwa kwabanye abantu lufakwe emiqulwini yocwaningo, angeke luqukethe ulwazi olobe lusho wean njengesiguli.

ILUNGELO LOKUNGENELA KWEZIGULI

Ukungenela lolucwaningo uyazi volontiyela. Uma uyela noma ngasiphi isikhathi alipheli ilungelo lakho lokulashwa.

Miss A Harrypaul	Dr J. K Adam	Dr R.B Dyer
Imgwaning/Umfundi	Ukusuphavaza	Ukusuphavaza
031 2099168	031 373 5291	031 2615031

INCWADI ENGIVUMA NGAYO UKUBAMBISANA KULOLUPHENUYO MFUNDO

Mina ……., igama eliphelele inombolo ye pasi …… ngifundile ngayizwa lencwadi ngokuphelele. Lapho nginombuzo khona, ngichazelwe ngu ……. nganeliseka. Ngaphezu kwaloko ngiuazi ukuthi ngingaphuma kuloluphenyo/fundo ngaphandle kokulimaza impilo yami. Ngakhoke ngiyazinikela, ngivuma ukuba omunye waloluphenyo, lokufunda.

Ufakazi igama …… **Sayina**……..

Ilanga nonyaka …….

Imgwaning/Umfundi igama…… **Sayina** ……..

Ilanga nonyaka …….

Isiguli igama ……... **Sayina** ……..

Ilanga nonyaka …….

Ukusuphavaza igama……... **Sayina**…….

Ilanga nonyaka …….

APPENDIX 2

ENROLLMENT

DEMOGRAPHICS

Procedure Date: _____(dd/mm/yyyy)
Name and surname: _____
Gender: M / F
Date of birth:____/___/_____
Age: ___

Vessel disease extent: ☐ 1 vessel ☐ 2 vessel ☐ 3 vessel

Please tick all tests done that suggest coronary artery disease or ischemia:

- ☐ ECG stress test (Treadmill)
- ☐ Nuclear Scan
- ☐ Resting ECG changes
- ☐ CT scan
- ☐ Stress Echo
- ☐ ST-Holter tape

ECG EVALUATION

Baseline ECG Yes ◯ No ◯

Post-procedure ECG Yes ◯ No ◯

BASELINE MEASUREMENTS

Heart rate at the beginning of the procedure: _____beats/min
Rhythm: _____
Blood pressure at the beginning of the procedure: _____mmHg
LVEF (calculated or estimated) (%) _____

APPENDIX 3

TARGET LESION INFORMATION

LESIONS

Number of lesions treated at this procedure: _____
Target vessel type: ☐ Native coronary artery
☐ Bypass graft

Number of stents implanted in this lesion: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
Main indication for intervention: _____
Stent type: _____

LESION DESCRIPTION

Reference Vessel diameter (visual estimate) (mm) _____
Lesion length (visual estimate) (mm)_____
Diameter stenosis (visual estimate):_____

LESION 1–STENT 1

Length _____mm
Diameter _____mm
Maximum pressure _____atm

Satisfactory result Yes ◯ No ◯ Suboptimal ◯

Post-dilation Yes ◯ No ◯

LESION 2–STENT 2

Length _____mm
Diameter _____mm
Maximum pressure _____ atm

Satisfactory result Yes ◯ No ◯ Suboptimal ◯

Post-dilation Yes ◯ No ◯

APPENDIX 4:

FOLLOW UP

FOLLOW UP CONTACT

Date of follow up _____(dd/mm/yyyy)
Type of Follow-up _____

Angina status of the subject
☐ Asymptomatic ☐ Angina pectoris ☐ Silent ischemia

Has any surgical procedure taken place since last contact? ☐ Yes ☐ No

Specify surgical procedure ◯ Elective ◯ Urgent

Specify type _____

MEDICATIONS AT THE TIME OF FOLLOW-UP CONTACT

Was aspirin treatment ongoing at the time of follow up contact?
☐ Yes ☐ No

If yes, was medication interrupted since last contact?
◯ Never
◯ Yes, for ≤ 5 days
◯ Yes, for ≥ 5 days

Aspirin interrupted
Specify main reason of discontinuation _____

If no, Specify: ◯ Never taken ◯ Discontinued

Aspirin Discontinued
Discontinuation date _____ (dd/mm/yyyy)
Main reason of discontinuation _____

Was clopidogrel treatment ongoing at the time of follow up contact?
☐ Yes ☐ No

If yes, was medication interrupted since last contact?
◯ Never
◯ Yes, for ≤ 5 days
◯ Yes, for ≥ 5 days

Clopidogrel interrupted
Specify main reason of discontinuation _____

If no, Specify: Never taken ☐ Discontinued ☐

Clopidogrel Discontinued
Discontinuation date _____ (dd/mm/yyyy)
Main reason of discontinuation _____
Was Ticlopidine started? ☐ Yes ☐ No
Start date Ticlopidine _____ (dd/mm/yyyy)

Was Ticlopidine treatment ongoing at the time of follow up contact?
☐ Yes ☐ No

If yes, was medication interrupted since last contact? ○ Never ○ Yes, for ≤ 5 days ○ Yes, for ≥ 5 days

Ticlopidine interrupted
Specify main reason of discontinuation _____

If no, Specify: ○ Never taken ○ Discontinued

Ticlopidine Discontinued
Discontinuation date _____ (dd/mm/yyyy)
Main reason of discontinuation _____
Was Clopidogrel started? ☐ Yes ☐ No
Start date Clopidogrel _____ (dd/mm/yyyy)

Anticoagulants
Anticoagulants
- Vitamin K antagonists (warfarin, coumadin, other)
- Oral thrombin inhibitors
- Other

Main indication
- Atrial fibrillation
- Prosthetic valve
- Cardiac emboli
- Pulmonary emboli or deep venous thrombosis
- Other

Diabetes treatment
☐ None ☐ Diet only ☐ Yes, oral antidiabetics ☐ Yes, insulin

Other cardiac medications:

Statins or other lipid lowering drugs	Yes	☐	No	☐	Unknown ☐
ACE inhibitors	Yes	☐	No	☐	Unknown ☐
Beta blockers	Yes	☐	No	☐	Unknown ☐

EVENTS

Did any of the following occur?

Cordis SES device failure	Yes	☐	No	☐
Procedural complications	Yes	☐	No	☐
Death	Yes	☐	No	☐
Myocardial infarction	Yes	☐	No	☐
Re-PCI	Yes	☐	No	☐
CABG	Yes	☐	No	☐
Stent trombosis	Yes	☐	No	☐
Bleeding	Yes	☐	No	☐
Cardio-vascular events	Yes	☐	No	☐
Cerebro-scular events	Yes	☐	No	☐
Other adverse events	Yes	☐	No	☐
Coronary angiography	Yes	☐	No	☐
If yes was it followed by Re-PCI	Yes	☐	No	☐
If yes was it followed by CABG	Yes	☐	No	☐

ADDITIONAL RELEVANT INFORMATION

_____
_____
_____
_____
_____
_____

APPENDIX 5:

MAJOR CARDIAC EVENTS

Death

Date of death _____(dd/mm/yyyy)
Please specify cause ☐ Cardiac death
☐ Non-cardiac death
☐ Unknown if cardiac or non-cardiac

If cardiac death, specify _____
If non-cardiac death, specify cause _____
Is there an evidence for stent thrombosis? _____

Is there evidence for MI? Yes ☐ No ☐
Did Re-PCI occur before the event? Yes ☐ No ☐
Did CABG occur before the event? Yes ☐ No ☐
Was an autopsy performed? Yes ☐ No ☐

Myocardial infarction

Date of MI _____(dd/mm/yyyy)

Please specify MI ☐ Q wave ☐ Non Q-Wave

Target vessel related to MI? Yes ☐ No ☐ Undetermined ☐

MI location? _____
Is there evidence for Stent thrombosis? _____

Did MI require CABG? Yes ☐ No ☐

Did MI require Re-PCI? Yes ☐ No ☐

Re-Percutaneous Coronary Intervention

Date of coronary angiography _____(dd/mm/yyyy)
Reason for coronary angiography _____
Specify main reason for Re-PCI _____

Is there an evidence for MI? ☐ Yes ☐ No

CABG

Date of last prior coronary angiography _____(dd/mm/yyyy)
Reason for coronary angiography _____
Date of CABG _____(dd/mm/yyyy)

Is there an evidence for MI? ☐ Yes ☐ No

Stent Thrombosis

Date of stent thrombosis _____(dd/mm/yyyy)
Specify timing after index procedure _____
Specify segment _____

Diagnosis is based on ☐ Angiography ☐ Autopsy ☐ Other

In your opinion what was the main cause of stent thrombosis?_____

Did stent thrombosis cause MI?	Yes ☐	No ☐
Did stent thrombosis require CABG?	Yes ☐	No ☐
Did stent thrombosis require Re-PCI?	Yes ☐	No ☐

Event Evaluation

Relationship to Cordis sirolimus-eluting stent

☐ Unrelated
☐ Unlikely
☐ Possible
☐ Probable
☐ Highly probable