PREDICTORS ON IN-STENT RESTENOSIS IN PATIENTS UNDERGOING PERCUATANOUS CORONARY INTERVENTION

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AUTHORS DECLARATION

This study represents original work by the author. It has not been submitted to any other Tertiary Institution. Where use of the work of others was made, it has been duly acknowledged in the text.

The research described in this dissertation was carried out in the Faculty of Health Sciences, Durban University of Technology under the supervision of Professor J.K. Adam (IREC Chairperson) and Dr Gafoor and Dr Soosiwala INC, Ethekwini hospital, Durban, South Africa under the supervision of Dr S Gafoor and Dr IU Soosiwala (Cardiologist, Durban Ethekwini Hospital).

SIGNED: _____

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I hereby certify that the above statement is correct.

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DEDICATION

I dedicate this work to:

My father and mother, for providing their children with a platform to succeed in all facets of life, for your love, encouragement and support have provided me with the confidence and perseverance necessary to achieve my goals.

To my brothers, and their families for their support and encouragement, when it comes to my career.

ABSTRACT

Introduction

Coronary artery disease is one of the leading causes of morbidity and mortality worldwide. The first percutaneous coronary intervention was performed by Andreas Gruntzig on September 16, 1977. This procedure was performed on patients with arterial stenosis. The limitations of angioplasty, however, included an unpredictable acute result- due to early abrupt vessel closure- and relatively high rate of restenosis at the site of the treated lesion- due mainly to plaque prolapse, vessel recoil, and constrictive remodelling. A vessel without a stent can have restenosis due to vessel remodelling as well as elastic recoil. Drug eluting stents have helped in the reduction of in-stent restenosis, but this still poses a problem for interventional Cardiologist. In-stent restenosis is an independent predictor for mortality during follow up, together with other relevant clinical factors as age, sex, diabetes mellitus, smoke habit, previous bypass surgery, and left ventricular ejection fraction.

Restenosis is not random; certain patients seem to present with this complication, having a better understanding of this phenomenon would be useful to save on financial cost of interventional cardiology as a result of adjuvant medication and devices. To establish the exact incidence of restenosis is not easy, it depends on a number of different factors and variables. These include patient related factors, lesion related and procedure related.

Drug eluting stents tend to drastically reduce the occurrence of severe neo-intimal proliferation, which is the dominant cause on in-stent restenosis. Optical coherence tomography (OCT) and intravascular ultrasound (IVUS) have played an important role in assisting with real time imaging of in-stent restenosis. Nevertheless, drug eluting balloons have been considered as the treatment of choice for in-stent restenosis.

The study aims to determine the predictors of in-stent stenosis in patients undergoing percutaneous coronary intervention and to recommend measures to reduce the incidence of in-stent stenosis.

This was a quantitative research study. It used the observational and descriptive retrospective approach focusing on patients who had in-stent restenosis after having percutaneous coronary intervention from June 2018 – February 2020. The study was conducted at a single practice called Dr Gafoor and Dr Soosiwala Inc. situated at the Ethekwini Heart centre, KwaZulu - Natal, Durban, South Africa. Permission to conduct the study was obtained from the hospital manager as well as the practice manager of Dr Gafoor and Dr Soosiwala Inc.

The data was collected through patient's files focusing on patients within the age group of 18 – 85 years.

Statistical analysis

The data was analysed using the SPSS Statistics 26.0 (Release August 2018) and Statgraphics centurion 15.1 (2006). The means standard deviation was analysed whereby a *p* value of less than 0.05 was considered statistically significant

Results

The collected data proved that the use of drug eluting stents improved the come backs of patients with in-stent restenosis, but this has not eradicated the problem. There has been a worldwide use of drug eluting stents being used in daily practice. Although management of drug eluting stent remains unclear, repeat percutaneous intervention remains the most frequently used treatment. Furthermore, baseline characteristics showed diabetic, hypertension and dyslipidemic patients had a higher risk of in-stent stenosis as compared to the other risk factors. (Diabetics 72%; hypertension 80% and dyslipidemia 78%). 4 out of 57 had acute and late stent thrombosis. 55% showed it was the left anterior descending artery that was affected most.

Restenosis can be regarded as a complex disease, whereby, the pathophysiological mechanisms are not fully understood. The study showed restenosis was higher in diabetics, hypertension, dyslipidemia and the type of artery affected. However, not much difference was found in other patient risk factors such as age and smoking.

This study correlated with other research findings found in the literature. Nonetheless, longer-term work is required and further imaging of vessels should be used as well as studies to prove if this will help with eliminating further in-stent restenosis.

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DEFINITION OF TERMS

Coronary Artery Disease (CAD)

Coronary artery disease occurs when there is a build-up of plaque in the coronary arteries. These coronary arteries supply the muscle of the heart.

Angina

Angina is a symptom of coronary artery disease and is a type of chest pain that can extend to the sternum to the arms, neck and jaws. It is caused by insufficient supply of blood to a portion of the heart.

Myocardial infarction

Occurs when there is a blockage of blood flow to the heart muscle which can lead to damage/ necrosis to the muscle of the heart.

Percutanous Transluminal Coronary Angioplasty (PTCA)

Angioplasty is a technique that is used to dilate or stretch opens a narrowing of a coronary artery with the help of a catheter with an inflatable balloon at its tip.

Coronary Stenting

Coronary artery stent is a small, metal mesh tubes or stainless steel metal plates. The stent is mounted on an angioplasty balloon catheter that is inflated to lock the stent against the coronary wall. These are referred to as bare metal stents.

Drug-eluting Stent (DES)

Drug-eluting stents that is drug-coated. The stent releases the drug into the vessel as well as the wall of the lesion. These stents have shown to significantly reduce the rate of re-blockage that occurs.

Intravascular ultrasound (IVUS)

Is a procedure where by a catheter is inserted into the coronary artery which has a camera at the tip of the catheter that allows you to view if there is plaque, calcification or clot in the artery.

Coronary Artery Bypass Grafting (CABG)

Coronary artery bypass surgery is a surgical procedure used to "detour" blood flow around blocked arteries. 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 and this bypasses the lesion.

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

IVUS: Intravascular ultrasound

OCT: optical tomography

ST: stent thrombus

STEMI: ST elevated myocardial infarction

LIST OF APPENDICES

CHAPTER ONE: INTRODUCTION

1.1 INTRODUCTION

Research findings have shown that coronary artery disease is one of the leading causes of morbidity and mortality worldwide (Byrne et al., 2015). Nonetheless, percutaneous coronary intervention procedure is used to help relieve clinical symptoms of angina and keep the coronary artery patent (Byrne et al., 2015). Progression of atherosclerotic disease in de novo coronary lesions, vascular injury sustained during percutaneous coronary intervention results in a complex inflammatory and reparative process that occurs over a relatively short time span. When there is excessive injury, restenosis occurs (Dean and Kim, 2011).

There is an increased confidence to use drug eluting stents for percutaneous coronary interventions and treat complex lesions, such as bifurcation lesions, left main stem lesions, chronic total occlusions, long lesions and multi-vessel disease. This is due to the fact that drug eluting stents in comparison to bare metal stents, tends to reduce the rate of in-stent restenosis (Kastrati et al., 2005). The use of bare metal stents (BMS) has been associated with in-stent restenosis, resulting as a significant complication of the procedure. According to Kastrati et al., (2005) drug eluting stents have contributed towards the reduction of in-stent restenosis, however, still poses as a problem for interventional Cardiologists.

Initially, reports of stent thrombosis occurring months, as well as sometimes years after the index percutaneous coronary intervention, tempered the promising results of DES early on (McFadden, Stabile et al., 2004). In-stent restenosis remains a critical drawback of coronary stents as well as a leading cause of unplanned, repeat procedures with the drug eluting stents (Magalhaes et al., 2014). In-stent restenosis may be defined as a gradual re-narrowing of a previously stented coronary artery lesion due to arterial damage, with subsequent neo-intimal tissue proliferation (Her and Shin, 2018).

The frequency of reported in-stent restenosis varies among different types of stents used, the lesion characteristics and the patient characteristics (Schwalm et al., 2013).

It has been reported via subsequent studies that the frequency of in-stent restenosis varies amongst the different types of stents that may have been used during the procedure, the lesion characteristics as well as patient characteristics. ISR occurs in about 15-35% of lesions treated with a bare mental stent the rate of ISR is usually lower following drug eluting stents implantation, and often less than 10%, but considerably higher when treating more complex lesions (Schwalm 2013).

This was a retrospective study of patients over a two-year period that had developed in-stent restenosis. The goal of this research study was to identify the causes of the in-stent restenosis. Thus, the researcher compared the clinical presentation, angiographic features and outcomes of DES –ISR among patients. Additionally, the primary objectives of the research study determined the cause of the in-stent restenosis whilst the secondary objectives assessed the occurrence of stent thrombosis, the need for repeat revascularizations and the occurrence of major adverse cardiac events (MACE) such as death. The various concerns surrounding antiplatelet therapy were also identified and addressed by the researcher. This includes but is not limited to, non-compliance of antiplatelet therapy and the time of development of ischemic events following stenting.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

2.1 STUDY BACKGROUND

2.1.1 The Heart

The organ which is responsible for pumping oxygen-filled blood to all parts of the body is the heart (Figure 1). It is the size of a first and consists of mostly muscular walls. A transport system of arteries, veins and capillaries carry the blood that is pumped from the heart, through the entire body. The pulmonary circulation is responsible for transporting blood from the heart to the lungs and vice versa. The systemic circulation is responsible for transporting blood from the heart to the rest of the body and vice versa. Therefore, the circulation of blood consists of two closed systems (Phate, 2008).

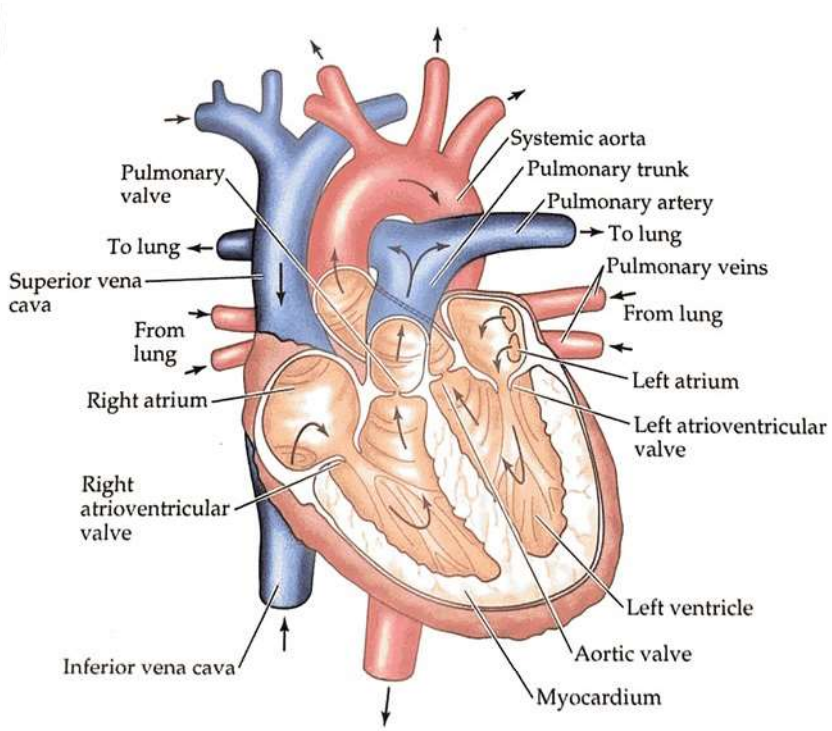

Figure 1: The heart's anatomy (cardiac catheterisation manual, 2014)

2.1.2 Pulmonary Circulation

The right atrium is the chamber of the heart which receives deoxygenated blood from the superior vena cava and the inferior vena cava. This blood then flows into the right ventricle through the tricuspid valve. The right ventricle then pumps the deoxygenated blood into the pulmonary artery, which divides into the pulmonary trunk, namely the right and left pulmonary arteries. They carbon dioxide present in the blood in the capillaries is removed and replaced with oxygen. The oxygenated blood is thereafter transported to the left atrium of the heart via the four pulmonary veins. The blood is thereafter pushed by the contraction of the left atrium through the bicuspid valve and into the left ventricle in order to be circulated throughout the body (Phate, 2008).

2.1.3 Systemic Circulation

The vascular structures act as conduits to carry vital oxygen and nutrients to each cell and also to carry away waste products. They also act as a control mechanism for maintaining the pressure in the heart and vessels. It is a complex interplay between the heart and the blood vessels that maintains adequate pressure and velocity within this system for optimal functioning (Cardiac catheterisation manual, 2014).

2.1.4 Coronary Circulation

The heart is a muscular organ which requires 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 present which surround the heart like a crown. The coronary circulation is a special branch of the systemic circulation. This allows the heart tissues and muscles to be supplied with oxygen and nutrients, and allows for the removal of wastes (Phate, 2008).

2.1.4.1 Right Coronary Artery (RCA)

The RCA arises from the right aortic sinus, which lies slightly inferiorly in comparison to the origin of the left coronary artery (Figure 2) and winds around in the right AV groove towards the crux of the heart. The first branch is usually the conus artery arising from the os. The second branch is usually the sinoatrial node artery. The mid portion of the RCA usually has several acute marginal branches supplying the anterior wall of the right ventricle. It also forms the posterior descending artery (PDA) in the posterior interventricular grove in about 80% of hearts making the RCA the dominant in these cases. The RCA supplies blood to the AV node in approximately 90% of the heart, supplies the right atrium and right ventricle, inferior and posterior wall and posterior portion of the inter-ventricular septum (Cardiac catheterisation manual, 2014).

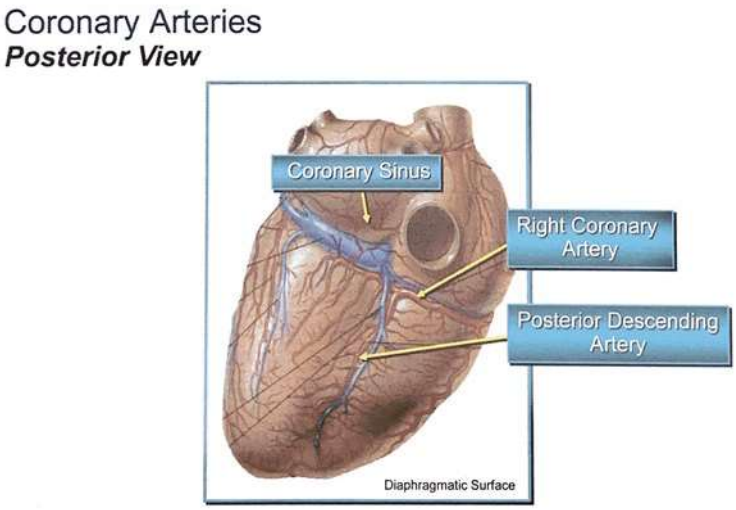

Figure 2: Right Coronary arteries (cardiac catheterisation manual, 2014)

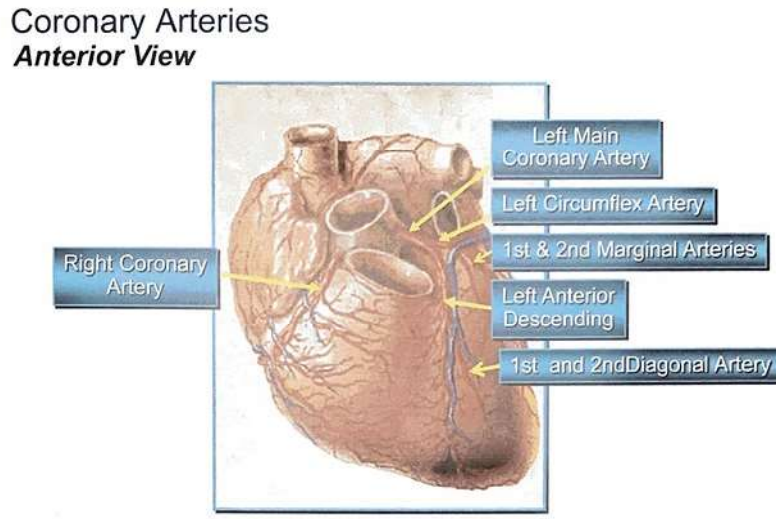

Figure 3: Left Coronary arteries (cardiac catheterisation manual, 2014)

2.1.4.2 Left Coronary Artery (LCA)

The origin of the LCA arises from the left aortic sinus and passes between the left auricle as well as the pulmonary trunk to reach the anterior atrio-ventricular groove (Figure 3). The sinoatrial nodal artery arises from the left system of the LCA. It thereafter ascends on the posterior surface of the left atrium to the sinoatrial node, in about forty percent of heart anatomy. There are two main branches which arise off the main coronary artery. These branches are known as the left anterior descending artery (LAD) and the circumflex branch (CX). The LAD courses down the anterior wall of the heart, thus earning its name. It encircles the cardiac apex and turns around at the inferior border of the heart. Here it will anastomose with the PDA of the RCA. The LAD is responsible for the blood supply of the anterior region of the left ventricular wall, parts of the right ventricle and the inter-ventricular septum. The LAD also gives rise to the diagonal branch (diag), which descends on the anterior surface of the heart. The diagonal branches vary in number from 1 to 3 and arise from the proximal LAD. Septal branches (3 to 5) arise at a right angle from the LAD and run within the right half of the septum to the posterior inter-ventricular sulcus. The smaller circumflex branch of the LCA follows the atrio-ventricular groove around the left boarder of the heart to the posterior surface of the heart. This artery supplies the

anterolateral region of the left ventricle and the region of the left atrium. The obtuse marginal (OM) branch of the CX follows the left margin of the heart and supplies the left ventricle. The posterior aspect of the heart is where the CX artery terminates (Phate, 2008).

2.1.5 Coronary Artery Disease

Coronary artery disease arises due to atherosclerosis (Figure 3). This may be defined as a variable combination of changes of the intima of arteries, which consist of a focal accumulation of lipids, a variety of complex carbohydrates, blood and related blood products, fibrous tissue and calcium deposits. It may also be associated with medial changes (Julian, Cowan and Mclenachan, 2004). A haemodynamically significant stenosis occurs when there is a fifty percent reduction in luminal diameter. This causes the smaller distal intramyocardial arteries and arterioles to be maximally dilated. Therefore, any increase in myocardial oxygen demand may provoke ischemia. There is a wide variety of clinical presentations for CAD, which range from relatively stable angina, unstable angina and myocardial infarction. Unstable angina and myocardial infarction fall under the umbrella of acute coronary syndrome (Clark and Kumar, 2009).

2.1.5.1 Plaque rupture

The development of a “mature” plaque doesn’t follow a uniform composition. It consists of a liquid centre which is a lipid in nature and is filled with procoagulant factors. A fibrous cap of connective tissue covers the top of the fluid centre (Figure 4).

Once the cap ruptures abruptly, there is a flood of procoagulant lipids into the vessel lumen causing platelet activation and local formation of a blood clot. Myocardial ischemia occurs as the clot blocks blood flow through the artery (Braunwald et al., 2001).

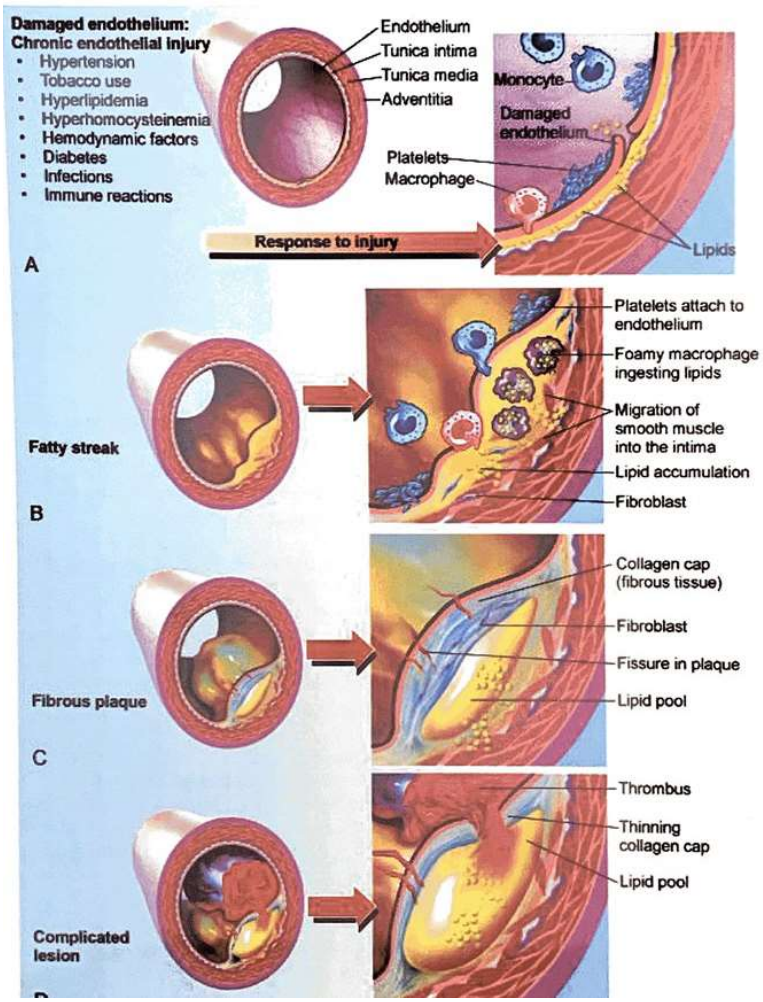

Figure 4: Coronary Artery Disease (Cardiac catheterization manual, 2014)

A: shows a normal artery with normal blood flow.

B: shows an artery with plaque buildup.

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. Tests used to diagnose coronary artery disease include:

-Electrocardiogram (ECG): This is an imperative diagnostic test that consists of 12 leads that allows you to assess how the heart generates and conducts electrical impulses. (Cardiac catheterization manual, 2014)

-Exercise Stress test: This test consists of a patient walking on a treadmill attached to a 12 lead ECG to view any ischemic changes. As one walks, the mycordial oxygen demand increases and changes develop if there is any stenosis.

-Imaging tests: Tests that takes detailed pictures of the heart, such as a chest x-ray, echocardiography or computed tomography.

-Blood tests: A test whereby they draw blood out of your body. These samples are then sent to a laboratory. There are certain blood markers that the examiner looks at to show if there is damage to the heart muscle.

-Cardiac catheterization: This is an invasive procedure that is used to diagnose and treat certain cardiovascular conditions. The examiner is able to visualise the coronary arteries more clearly using contrast and imaging. This is performed whereby a long thin tube called a catheter is inserted in an artery that leads to the heart (Cardiac catheterization manual, 2014).

2.1.5.2. Treatment of coronary artery disease options:

2.1.5.2.1 Options of Medical Treatment for CAD

The aim of treatment is to improve the quality of life by reducing the occurrence of and severities of angina attacks, as well as reduce the risk of death or nonfatal myocardial infarction. Some of the medications that may be prescribed by the Doctors to control symptoms and, in some cases, slow the progression of CAD:

-Antiplatelet medications such as aspirin 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 do not work. Unlike other medicines used to treat angina, ranolazine does not 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).

2.1.5.2.2 Coronary Artery Bypass Surgery

Coronary artery bypass grafting (CABG) is defined as “open heart surgery in which a portion of the vessel is grafted from the aorta to the coronary artery to bypass the blocked section of the coronary artery and improve the blood supply to the heart” (Diodato 2014; Chedrawy; 2014). Heart surgery in the 19th century had poor results post bypass due to it being performed infrequently. Cardiac surgery became more feasible after the development of the heart lung machine.

Re-establishing perfusion to the myocardium is the main goal of CABG. A systemic review of studies comparing CABG with POBA or PCI concluded that survival was similar for single and multivessel disease. The incidence of MI was similar for both. CABG patients had more relief of angina symptoms than PCI and repeat revascularisation was required less after CABG than PCI (Diodato 2014; Chedrawy; 2014).

2.1.5.2.2.1 Saphenous Vein Grafts

Post CABG surgery, atheromatous degeneration may occur within a saphenous vein graft (SVG) leading to recurrent ischemia in most cases. With SVG intervention, outcomes are shown to have improved with BMS as compared to balloon angioplasty. DESs are found to further lower the rate of restenosis. Due to the calibre of SVGs, the tolerated late loss is generally greater than native coronary vessels and disease progression is more frequent (Topol and Teirstein, 2016).

Two hundred and twenty patients were randomly assigned to take part in the saphenous vein graft de novo trial (1997) for treatment with Palmaz-Schatz stent placement or, PTCA alone. There was a higher procedural success rate noted with stenting although this came with more bleeding events due to the extensive and aggressive anticoagulation therapy used in the study. The rate of restenosis was not found to be significantly lower in those patients treated with stent placement rather than PTCA alone, but it was found that the stent group was shown to have better outcomes in terms of significant cardiac events. Therefore, stents are preferred rather than PTCA alone for patients with ostial or body SVG lesions (Savage.et al., 1997).

2.1.5.2.3 Percutaneous Transluminal Coronary Angioplasty (PTCA)

The first procedure of balloon angioplasty or PTCA was performed in 1977 by Andreas Gruentzig using a prototype of a fixed-wire balloon catheter. PTCA allows the atherosclerotic plaque to be redistributed along its longitudinal axis by stretching and tearing the plaque and vessel wall resulting in expansion of the coronary lumen (Figure 5). This procedure may be performed under local anaesthetic in the cardiac catheterization laboratory using one of three techniques to gain access: the femoral, brachial or radial route. A guide catheter is inserted using the desired route and is positioned at the coronary ostium. A steerable guide wire is thereafter passed through and guided past the stenosis into the distal segment of the artery. The guide wire remains in the vessel as it keeps the position and allows the stent and balloon to be guided through to the correct position. A dilation catheter is passed through, over the guidewire and the balloon is positioned at the position of the stenosis.

Multiple inflations will allow splitting of the atherosclerotic plaque at its weakest point. Afterwards, the dilation catheter and guide wire are removed from the vessel and the enlarged lumen may now be visualized and evaluated via coronary angiography (Giuliani et al., 1996).

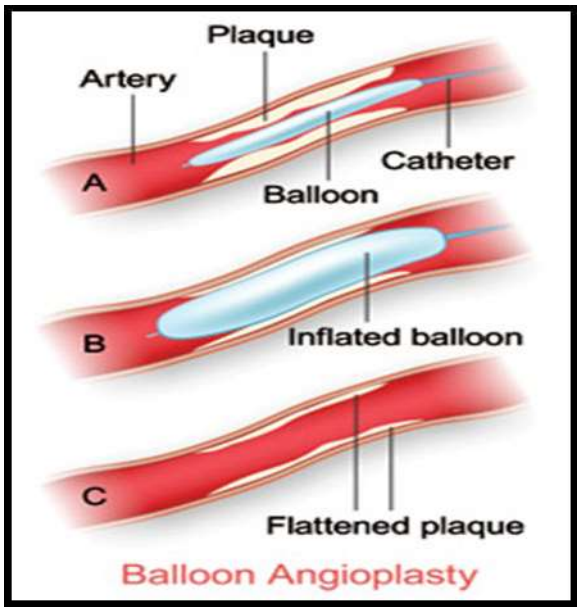

Figure 5: Balloon angioplasty

(http://www.texasheart.org/HIC/Topics/images/fig15_ptca1_3.jpg)

This procedure was initially limited in use and introduced as an alternative to CABG. Less than ten percent of patients were given this opportunity, only if they had symptomatic CAD and just a single, non-calcified, focal lesion in a proximal coronary vessel. Over time, especially over the next decade, there was a rapid evolution in terms of equipment design and operator experience which allowed a broader spectrum of patients to undergo this procedure. This included patients with multivessel disease, a complex and challenging anatomy, reduced left ventricular function and those with serious comorbidities. Although strides were made in the improvements of these procedures and equipment, two major complications hindered the widespread use of PTCA. Firstly, the treated vessel may undergo abrupt closure which was found to occur in five to eight percent of cases, therefore

requiring emergency CABG in three to five percent of cases, usually within six to nine months after the initial procedure. The second complication which occurred in fifteen to thirty percent of patients was the restenosis of the treated lesion, which allowed previous symptoms to reoccur, usually within six to nine months after the initial procedure (Baim et al., 2005).

This led to the development of a series of new coronary devices in the early 1990's which served a way forward, to improve on the initial procedural outcomes achieved with PTCA. Coronary stenting was found to be consistent in its improvement of procedural safety and clinical outcomes, as compared with balloon angioplasty in patients undergoing routine percutaneous coronary intervention. Despite this, balloon angioplasty still remains an important aspect of the procedure, whether it may be prior to stent placement in order to pre dilate a vessel, during stent placement in order to deploy a coronary stent or to post dilate a stent after it has been deployed (Baim, Kuntz and Popma, 2008).

2.1.5.2.4 Percutaneous Coronary Intervention

The value if percutaneous coronary intervention or surgical revascularization lies in the relief of symptoms of ischemic coronary artery disease. This has led to an expansion of the use of PCI to treat CAD. Various improvements made have led to an increase in the procedural safety, success and durability of the procedure. This has occurred due to continuous improvements and refinements in the technological aspects of the procedure, refined pharmacological guidelines and a clearer understanding of procedural outcomes, early and late. This led to increased support for the use of percutaneous coronary intervention for ischemic CAD therapy (Baim et al., 2005).

2.1.5.2.4.1 Outcomes following Percutaneous Coronary Intervention

Outcomes after a procedure are usually measured by the procedural success as well as complication rates. Early success (<30 days) depends the safety and effectiveness of the procedure and can be measured as relief of angina; freedom

from myocardial infarction; freedom from death or urgent revascularization. Late success (30 days – 1 year) depends on the progress of atherosclerosis on remote sites and clinical restenosis. This can be measured as relief from recurrent angina, freedom from myocardial angina or death and revascularization of the target vessel (Smith et al., 2006).

2.1.5.2.4.2 Early Clinical Outcome

Once the procedure has been able to attain a residual diameter stenosis of less than 20 percent as well as relief from ischemia and improvement in the diameter of the vessel, the procedure may be referred to as an angiographic success. A successful procedure is defined as a successful angiographic procedure without any major complications within 30 days of procedure (Topol and Teirstein, 2016). Clinical success may be defined as a successful angiographic procedure which does not require the need for repeat or urgent PCI or the need for surgical revascularization within 30 days following the procedure (Topol and Teirstein, 2016).

Minor and major complications may occur due to the procedure. Minor complications could be vascular complications, transient ischemic attacks; nephropathy induced by contrast use or a number of different angiographic complications. Major complications include stroke, myocardial infarction or death; however mortality after PCI remains at less than 1 percent. It may usually occur in patients with cardiogenic shock, poor left ventricular function with an occlusion or ST elevation myocardial infarction (Califf et al., 1998). One of the most common complications to arise from percutaneous coronary intervention remains periprocedural myocardial infarction.

There are two classification systems that are used in order to classify myocardial infarction occurring after percutaneous coronary intervention. According to the World Health Organization, myocardial infarction is defined as an elevated creatine phosphokinase isoenzyme (CPK) more than two times its normal value as well as an elevation of the CPK-MB isoform. Therefore, periprocedural myocardial infarction does occur in 1-2 percent of cases following percutaneous coronary intervention. According to the FDA classification system, an elevation of CPK-MB of three times or more of the normal value defines a myocardial infarction (Califf et al., 1998).

Periprocedural myocardial infarctions may also arise due to various complications that may occur during stenting, dependant on their severity and duration. In the case of coronary dissections, clinical ischemia may develop if the dissections extend deeper into the vessel, such as the media or adventitia and compromise the true lumen of the vessel (Smith et al., 2006). Most dissections occurring during a procedure can be treated immediately with stenting, but there may be significant residual dissections that may occur in 1.7 percent of patients. This increases the risk of myocardial infarction occurring post procedure, as well as may warrant an emergency CABG. The occurrence of stent thrombosis will therefore likely increase the mortality rate threefold (Smith et al., 2006).

2.1.5.2.4.3 Late Clinical Outcome

In 10 to 20 percent of cases following stent implantation, clinical restenosis is attributable to the occurrence of intimal hyperplasia within the stent (Baim, Kuntz and Popma, 2008). In 3 to 5 percent of cases following the implant of a drug-eluting stent, clinical recurrence is due to focal tissue growth occurring within the stent or at the margins of the stent (Baim, Kuntz and Popma, 2008). Progression of atherosclerosis may occur within a coronary vessel at a remote site from the treated area and this may exacerbate clinical symptoms after percutaneous coronary intervention. A remote plaque rupture may also result in death or myocardial infarction after the initial procedure and intervention. The timing of these occurrences partially allows us to distinguish between these processes. Usually, within 6 to 9 months of the intervention, clinical restenosis may occur due to re-narrowing of the lumen occurring at the initial site of stenting. A low but constant risk remains (about 1-2 percent a year) for death and myocardial infarction to occur due to plaque instability at any given time after the intervention. Certain predictors are present for the higher risk of late mortality. These may include congestive heart failure, an advanced age, impaired left ventricular function, diabetes mellitus, increased number of diseased vessels, progressed disease which is inoperable and severe comorbid conditions. The various risk factors present for instent restenosis may include age, diabetes mellitus, a longer total stent or lesion length, small lumen diameters despite

intervention and the presence of a lesion on the left anterior descending artery (Baim, Kuntz and Popma, 2008).

2.1.6 ST elevated Myocardial Infarction (STEMI)

The instances leading to an acute ST segment elevated myocardial infarction (STEMI) involve the rupture of an atheroma consisting of a thin cap, a lesion consisting of a necrotic core rich in lipid as well as a fibrous cap overlying the lesion which is thin and inflamed. Once the release of tissue factors and prothrombotic constituents occurs, which results in a thrombotic occlusion occurring within the coronary vessel followed by myocardial necrosis. The myocardium may be improved or salvaged by timely reperfusion brought about by PCI (Topol and Teirstein, 2016). Stent implantation may result in delayed endothelialization as well as high rates of stent thrombosis.

The advantage that primary stenting allows us in regards to PTCA for STEMI is the prevention of arterial remodelling that occurs due to PTCA and the subsequent scaffolding of the ruptured plaque (Grines et al., 1999).

2.1.7 Acute Coronary Syndrome

There are multiple risk factors present which continue to display increasing rates of restenosis as well as late lumen loss, posing a significant clinical problem. Various drug treatments are present (such as statins, calcium channel blockers, antiplatelet drugs, angiotensin converting enzymes) although they have been unsuccessful towards reducing the neointimal proliferation effectively. Acute coronary syndrome is prevalent in ISR patients as much as 60-70% of the time and MI is prevalent 5-10% of the time (Cho, 2017). A different study showed that patients who present with ACS and ISR were generally older in age, mostly female, with a higher occurrence if diabetes, hypertension, had previously undergone CABG and were under tobacco use (Cho, 2017).

2.2 LITERATURE REVIEW

2.2.1 Coronary Stents

Stents are designed in such a way in order to maintain patency of a vessel after revascularization of a diseased coronary vessel. The cylindrical mesh scaffold of a stent is mounted in a collapsed state on a balloon catheter. Inflation of the balloon causes expansion of the stent which causes it to push against the coronary artery vessel wall and blockage (Figure 6). This will maintain vessel patency after deflation and removal of the balloon.

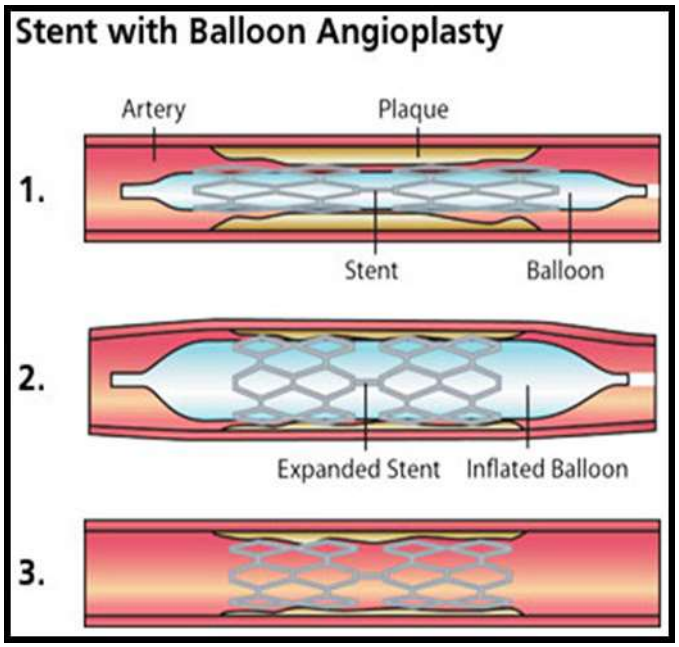

Figure 6: Coronary stenting (http://www.cts.usc.edu/graphics/stent.jpg)

Stents assist by optimising the gain of the lumen, preventing early recoil of the vessel and limiting the adverse effects of late vessel remodelling. Since the 1990s, stents have revolutionized the process of PCI. Stents are also found to restrain dissection flaps and assists in creating a regular and sound smooth vessel lumen. This reduces the chance of occlusion of the vessel (Kassimis and Banning, 2016).

Studies have been conducted in order to investigate the safety as well as the efficacy of bare metal and drug eluting stents. It has been found that first and second

generation of drug eluting stents are proven to be safer and superior to bare metal stents (Palmerini et al., 2015).

2.2.1.1 Stent design

Coronary artery stents may be classified based on:

- Composition: this could be metallic or polymeric
- Configuration: such as bioabsorption
- Coatings: such as heparin, polytetrafluoroethylene (PTFE), paclitaxel, sirolimus etc.
- Self-expandable or balloon strut expandable stents.

2.2.1.2 Bare metal stents

In 1986 researchers Ulrich Sigwart, Jacques Puel, and colleagues implanted the first peripheral and coronary stent in a human. Thrombotic occlusion and late mortality was found in eight of their patients who had stents implanted. Although patients without thrombosis had shown an angiographic restenosis rate of only 14% after 6 months, for the first time, it was shown that stenting could improve late patency and stabilize acute results over plain old balloon angioplasty, (Topol and Teirstein, 2016).

After this, many bare metals stents were developed and used to improve the deliverability as well as struts modification in order to reduce the in-stent restenosis rate. Despite the success of baremetal stents being used this was hindered by stent thrombosis and this necessitated an intense antithrombotic and antiplatelet regimen. Overall modification of stent struts and the use of pharmacotherapy regimens over the early 90s helped reduce the stent thrombosis rate by 1 -2%. By late 1990s baremetal stenting had become the treatment of coronary artery disease (Topol and Teirstein, 2016).

2.2.1.3 Drug eluting stents

Drug eluting stents (DES) were first introduced in 2002, since then this has reduced the rate of in-stent restenosis and the need for repeat revascularistaion. There is different generation of drug eluting stents which is the first, second, third and fourth generation. The first generation DES composition consisted of a stainless steel mesh with a slotted tube design; these stents are drug coated with sirolimus (Cypher) and paclitaxel (TAXUS). This reduced the neointimal proliferation and restenosis.

The second generation DES consisted of zotarolimus-eluting (endeavour) and everolimus- eluting (Xience V) stents. These drugs helped with long-term safety and anti-restenotic efficacy.

The third generation stents were composed using biogradeable polymers. The ION stent (Boston Scientific) is a platinum chromium platform, poly –based paclitaxel-eluting stent.

Fourth generation stents are composed of bioabsorbable and polymer-free DES. Biofreedom (Biosenseors), VESTA sync (MIV therapeutics) are examples of polymer-free DES (Domb and Khan, 2014).

A study that was conducted by Dangas et al., (2010) showed that since the introduction of drug eluting stents there has been a reduction in in-stent restenosis after intervention of the artery. The use of drug eluting stents had then become the standard practice, this brought about a new problem as this showed a 3% to 20% increase in in-stent restenosis. The reason for this in-stent restenosis was due to lesion characteristics, type of stents used and patient risk factors (Dangas et al., 2010).

A previous study was done to compare in-stent restenosis across three stent generations and this shows that irrespective of the type of stents used, the clinical presentation of ISR remains similar. ISR presenting as myocardial infarction seemed to be associated with patient-related factors and not device-related factors. The lower likelihood of second-generation drug eluting stent ISR presenting as MI may be the net benefit of reduced hyperplasia and less vulnerable neointimal tissue (Magalhaes et al., 2014).

2.2.1.4 Dual Drug Eluting Stent

The introduction of a dual DES was done in order to promote stent-based therapies which may assist in reducing neointimal hyperplasia as well as promote healing of the endothelium (Domb and Khan, 2014). Currently, with the dual DES delivery system, two drugs are delivered simultaneously. The first drug is released for the first two weeks with the intention of preventing proliferation of the vascular smooth muscle cell. Thereafter, the second drug is delivered after a month or so in order to promote re-endothelialisation (Domb and Khan, 2014).

2.2.2 Restenosis after percutaneous coronary intervention

Restenosis is a condition identified by recurrent ischemic related events for which the causative mechanisms have not yet been fully identified. Stents have been found to induce more arterial injury than balloon angioplasty, and this may result in greater neointimal hyperplasia development 6 to 12 months after the procedure. The vascular response evoked by vascular damage during coronary intervention is thought to be the main contributor to the development of restenosis (Dean and Kim, 2011).

2.2.3 Pathophysiology

The inflammatory responses to the endothelial denudation and subintimal hemmorhage caused by the balloon or stent may result in the onset of several proliferative processes. These include vascular smooth muscle cell (VSMC) proliferation and migration, extracellular matrix formation and neointimal hyperplasia.

Stent fracture is another factor related to restenosis. Stent fracture involves exposure of the stent to compression, torsion, bending and shear stress brought about by repetitive cardiac contraction resulting in mechanical fatigue. The underexpansion of a stent may be a reason for stent vessel recoil which is related to the procedure (Jukema, 2011; Verschuren et al., 2011).

2.2.4 Restenosis

Restenosis is a narrowing of the lumen done by an increasing acute luminal gain, as well as elimination of late recoil and negative vessel remodelling. The use of BMS reduced the rate of instent restenosis when compared with balloon angioplasty (Topol and Teirstein, 2016). In relation to research findings, stents induces more arterial injury which results in a greater amount of neoimtimal hyperplasia development over the first 6 to 12 months following the procedure, thereby resulting in binary angiographic restenosis in 10% to 50% of lesions, depending on patient and lesion complexity (Topol and Teirstein, 2016). Most commonly, following a year of stent implantation, patients were presenting with stable angina and exercise induced ischemia for restenosis. It has now become more recognized as ACS and occasionally STEMI in about 25% of patients.

Numerous studies conducted after BMS implantation demonstrate that the presence of diabetes mellitus, small RVD and longer lesion lengths are the cases mostly reproducing instent restenosis (Topol and Teirstein, 2016). The other factors present are cases in which the lesion is located at the ostium of the artery, calcific lesions, bifurcating lesions, chronic total occlusions (CTO) or even those lesions located in a saphenous vein graft (SVG). These factors also contribute to instent restenosis with DES.

DES use has been shown to reduce target lesion revascularization (TLR) compared with BMS use. These also included SVG lesions with a recent randomized trial showing lower rates of restenosis with DES compared with BMS in this subset of lesion (Topol and Teirstein, 2016).

Nonetheless, the largest randomized trial to examine this tissue, the sirolimus-eluting stent (SES) versus paclitaxel-eluting stents (PES) for coronary revascularization (SIRTAX) trial showed incremental late loss in both stents (Topol and Teirstein, 2016). This indicates that clinical results are unknown.

The cause of restenosis after stenting is multifactorial and may be brought about by excessive late neointimal hyperplasia. Restenosis may also occur with the use of BMS or DES in cases where the stent has been underexpanded, there may be some

residual untreated disease, and there may be a dissection at the edge, a geographic miss or stent fracture (Topol and Teirstein, 2016).

Literature demonstrates that patients who develop in-stent restenosis are at higher risk of repeat restenosis after percutaneous treatment, especially if there is a diffuse pattern of restenosis. IVUS and OCT imaging has been beneficial in distinguishing between neointimal hyperplasia from under expanded stents, geographical miss, fracture of the stent strut, and other rare occurrences which may occur such as embolization of the stent and chronic recoil (Topol and Teirstein, 2016). Therefore, it can be argued that the use of these modalities during the procedure may minimise in-stent restenosis.

2.2.5 Clinical Risk factors for restenosis

Researchers have found that diabetes mellitus is one of the most consistent clinical parameter that increases the risk of restenosis (Dean and Kim, 2011). This study is consistent with a study by Jukema et al., (2011) which showed that patients with insulin dependent diabetes are at particular high risk of adverse events following PCI.

Another study revealed that patients with diabetes mellitus (DM) are at higher risk of in-stent restenosis due to increased inflammatory response, endothelial dysfunction, excessive neointimal hyperplasia and hypercoagulability (Buccheri et al., 2016).

However, only a limited number of studies showed that diabetes is not a contributing risk factor in drug eluting stents, whereby others found an increased risk. It was found that diabetics had a high prevalence for stent edge restenosis (Paramasivan et al., 2020). Age, gender and hypertension seem to be inconclusive in association with in-stent restenosis. A clinical factor applicable to the entire coronary system is history of restenosis. Several studies have shown that cigarette smoking is associated with a lower rate of restenosis as it has a protective effect (Jukema 2011; Verschuren et al., 2011).

2.2.6 Risk factors related to lesion and procedure

A recently published study showed that among the known risk factors for CAD, the site and length of stent implanted as inflammatory markers on the ISR, hypertension and diabetes are two factors that make them more likely to be discussed as a contributing factor. Other factors such as smoking, old age, and length of the stent are also of importance in the incidence of ISR (Sajadian, 2018; Alizadeh et al., 2018).

Several lesion characteristics have shown to increase restenotic risk, e.g., the longer the length of the lesion, the higher the risk. Small vessel diameter and a minimal lumen diameter after stenting are very important to note as these add to increased risk to restenosis. Other contributing factors that play a role in in-stent restenosis are multiple stents and stent underexpansion of stents during PCI. A history of restenosis increases the risk of a subsequent episode of restenosis (Jukema, 2011; Verschuren et al., 2011).

Another study showed that in postoperative levels of hs-CRP and HCY, history of diabetes, stent length and bifurcation type lesions are independent factors of in-stent restenosis (Cheng, 2019; Chang et al., 2019).

Although studies have shown IVUS guided PCI reduces the rate of in-stent restenosis, further studies need to prove this.

2.2.7 Treatment of restenosis

In-stent restenosis is a benign condition and may present with either STEMI or ACS. Patients that develop in-stent restenosis require revascularisation to relieve symptoms (Topol and Teirstein, 2016).

2.2.8 DES restenosis

Superiority of DES over BMS has been demonstrated through multiple trials which have been conducted regarding clinical end points such as revascularization of the target vessel/ lesion. Initially, reports of DES use haven’t shown a detectable rate

following implant and follow up, short or long term (Kim and Dean, 2011). The mechanism of DES failure remains a controversial topic especially with certain patients and lesions. Multiple variables such as biological/ clinical, mechanical as well as technical may be involved and multiple factors may be present (Kim and Dean, 2011).

Nonetheless, stent placement carries the risk of stent thrombosis which results in a myocardial infarction and could result in mortality within 30 days in 10-25% of patients. Optimal reperfusion may be achieved by repeat PCI for the treatment of ST.

ST is considered to be acute if it occurs within the first 24 hours; subacute if it occurs between 1 and 30 days; early if it occurs within the first 30 days; late if it occurs between 30 days; and a year, and very late if it occurs after 1 year. ST is also classified as primary if it is related to the implant stent or secondary if it occurs at the stent-site after an intervening target lesion revascularization (TLR) procedure for restenosis.

The mechanisms that underlie ST are multifactorial and include patient; lesion; procedure and stent related factors. ST occurs frequently in complex lesions, especially in patients with acute coronary syndrome and thrombotic lesions, diabetes, and small vessels.

Early ST thrombosis is related to procedural factors such as stent expansion, dissection and residual disease at the stent margins. IVUS has proved to be a useful tool in identifying these factors (Kim and Dean, 2011).

Table 1 shows the established risk factors associated with stent thrombosis and the consequences of these factors towards the human body.

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

2.2.9 Total Coronary Occlusions

It has been found that the rates of restenosis clinically and angiographically are higher following both balloon angioplasty and stent implantation for PCI of a chronic total occlusion (CTO) when it is compared with a stenosis that is non-occluded. This may be due to a greater occurrence of diabetes and lesion length plaque mass (Topol and Teirstein, 2016). There have been a large number of studies conducted comparing DES and BMS retrospectively and non-randomised. They have shown a reduction in clinical restenosis of approximately 60%. There has also been results shown of improved outcomes based on observational studies done comparing the use of a second generation DES to a first generation DES for CTO lesion treatment (Topol and Teirstein, 2016).

2.2.10 Bifurcation lesions

Around 20% or more of cases that have undergone stenosis requiring angioplasty are bifurcation lesions. These may be associated with increased complications encountered during the procedure as well as worsening long-term outcomes. There have been increased rates if clinical restenosis occurring at bifurcating lesions, therefore the standard of care has become the use of a DES for the main vessel (Topol and Teirstein, 2016).

Therefore, the process of how bifurcation lesions contribute to in-stent restenosis is due to the increased number of balloons and inflations that are performed, which then leads to aggravation of vascular endothelial dysfunction. This concurs with a study by Cheng and Chang (2019) which showed coronary bifurcation lesions as independent risk factor of in-stent restenosis.

2.2.11 Antiplatelet Therapy

The use of one or more antiplatelet agents combined is a requirement for percutaneous coronary intervention, as the inhibition of thrombus formation is required to prevent thrombus on the stents used during the procedure (Rosano and Seferovic, 2018). The standard strategy to prevent thrombus formation on the stent is currently the use of aspirin and thienopyridine (such as Plavix) (Rosano and Seferovic, 2018).

There have been intensive debates worldwide regarding the safety of the use of DES and the duration of dual antiplatelet therapy required following stent implantation. Currently, the guidelines set internationally have a recommendation that following DES implantation, dual antiplatelet therapy should be initiated for duration of 6-12 months. In the case of acute coronary syndrome, dual antiplatelet therapy should be initiated for 9-12 months (Rosano and Seferovic, 2018).

It has been found that there is a growing need of a more individualized regimen for antithrombosis, especially for patients with an additional requirement for anticoagulation, or those due for urgent surgery that may not be cardiac-related within the time frame of their antithrombotic regimen, or even those that are not

responsive to clopidogrel. The adjusted antithrombotic therapy needs to take into account the patient's risk of severe bleeding complications as well as duration and intensity of treatment required (Topol and Teirstein, 2016).

Aspirin can be defined as an irreversible inhibitor of the enzyme cyclooxygenase that blocks the synthesis of thromboxane A2, a vasoconstricting agent that promotes platelet aggregation (Baim, Kuntz and Popma, 2005). 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. The combined use of aspirin and thienopyridine is shown to be more beneficial to inhibit platelet aggregation and stent thrombosis due to their synergistic properties and mechanisms of action rather than when used alone (Baim, Kuntz and Popma, 2005).

The Bern and Rotterdam cohort study, a large two-institution study consisting of 8146 patients undergoing implantation of a DES documented late stent thrombosis to occur at a rate of 0.6% constantly, per year, for 3 years following implantation. Late stent thrombosis in this case was defined as occurring more than 30 days following percutaneous coronary intervention (Daemen et al., 2007). Depending on the type of drug eluting stent implanted at Rotterdam, patients were required to receive clopidogrel for 3 to 6 months. At Bern, patients were required to receive clopidogrel for 12 months as well as aspirin, irrespective of the type of drug eluting stent used. With the Rotterdam study, it was found that patients who did experience late stent thrombosis, 51% had only received one antiplatelet drug, 26% were found to not be on any type of antiplatelet therapy, and 30 out of 31 patients who were only receiving aspirin experienced stent thrombosis but only after their clopidogrel prescription had expired. Therefore, the absence of clopidogrel use was found to not be a predictor of stent thrombosis overall (Daemen et al., 2007).

Similar results were yielded in a study conducted by Duke University of The United States of more than 4600 patients (Daemen et al., 2007). Follow up of patients was conducted at 6 months, 12 months, and 24 months in order to assess for death or non-fatal myocardial infarction. Patients who discontinued the use of clopidogrel after the implantation of drug eluting stents encountered more than twice the risk of myocardial infarction or death, compared to patients who diligently followed their prescription. The risk compared over 18 months was 7.2% versus 3.1%. These

findings therefore illuminate the beneficial effect of prolonged antiplatelet therapy for drug-eluting stents (Eisenstein et al., 2007).

Interruption of antiplatelet therapy for patients to undergo non-cardiac surgery carries its own risks. Interruption of therapy early after stent implantation may have fatal consequences and an increased risk of stent thrombosis. The mortality rate of such patients was in the range of 2.5-21.4% as found in an analysis of eight observational studies conducted (Chiche et al., 2007). Therefore, possibly, if one could delay elective non-cardiac surgery in patients who have had recent coronary stent implantation, they will reduce the risk of stent thrombosis (Chiche et al., 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.

CHAPTER 3: MATERIALS AND METHODOLOGY

3.1 Introduction

It has been proven that the use of drug eluting stents improves the come backs of patients with in-stent restenosis, but this has not eradicated the problem (Her and Shin, 2018). There has been a worldwide use of drug eluting stents being used in daily practice. Although management of drug eluting stent remains unclear, repeat percutaneous intervention remains the most frequently used treatment (Her and Shin, 2018).

3.2 Study design

This study used a quantitative form of research approach. Quantitative studies can be understood as a collection of data. That being said this form of approach was perceived as befitting this research study as patients had presented to us after the angiogram with in-stent restenosis. It is an observation, descriptive retrospective study of patients who were found to have in-stent restenosis after having percutaneous coronary intervention or previous PCI within the time period June 2018 until February 2020.

3.3 Study setting

This research study was conducted at a single practice, Dr Gafoor and Dr Soosiwala INC at Ethekwini Heart centre, KwaZulu-Natal, Durban, South Africa.

Permission to conduct the research study was obtained from the hospital manager as well as the practice manager of Dr Gafoor and Dr Soosiwala Inc.

3.4 Sample

This study had a sample size of 57 patients. The reason it was 57 patients over a two year period is that we don't expect to have patients present with blocked stents but this seems to be an on-going issue.

3.5 Target Population

Data was collected from the patient files of all adult patients between the age of 18 to 85 years that had been diagnosed with in-stent restenosis who were referred to Dr Gafoor and Dr Soosiwala Inc at Etekwini Hospital.

The mission 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 include complete cardiovascular medical exam, electrocardiograms and treadmill testing. We also provide invasive cardiology services which include coronary angiography and angioplasty of the coronary arteries.

3.6 Inclusion criteria

-Patients who have undergone percutaneous coronary intervention that present with clinical symptoms and underwent an angiographic in-stent restenosis.

-Patients residing in KwaZulu-Natal.

3.7 Exclusion criteria

-Patients who presented with an ejection fraction < 25%, were excluded. Ejection fraction is a measurement of the volumetric fraction of blood ejected with every beat of the heart.

-Patients who also presented with cardiogenic shock were excluded; this is a condition whereby the heart cannot pump blood to all vital organs of the body.

3.8 Limitation

There were several important limitations of the study. The sample size was small. The study was limited to a Cardiologist's practice which compiled of two Cardiologists.

3.9 Patient recruitment

All patients who had in-stent restenosis were enrolled into the study. The patients were then examined by Dr Gafoor or Dr Soosiwala.

1.) The patient data was collected post procedure. Demographic data of patients and cardiac history were collected from review of the doctor's notes and the patient's chart

2.) Angiographic features and procedural data were obtained from the radiographer

3.) Procedural characteristics were obtained from the clinical technologist notes. Type or location of lesion, reference vessel diameter, lesion length and maximal balloon pressure were variables included in the list. In addition, the number of stents implanted was included.

All parameters collected are on Appendix A.

3.9.1 Informed Consent

All patients that have an angiogram signed an informed consent for the procedure.

3.10 Data collection

The researcher assessed and collected the demographics, angiographic and clinical characteristics of all patients with the following data being collected from patient files:

3.10.1 Medical history

The Cardiologist took a detailed medical history of the patient which was documented. This entailed a detailed history of symptoms experienced as well as a clinical examination performed.

3.10.2 Demographics

The age, sex and race of each patient enrolled were documented.

3.10.3 Clinical parameters

-Hypertension is abnormally high blood pressure. It is an arterial pressure of above 140/90mmHg. Globally, 51% of strokes and 45% of cases of ischemic heart disease are attributable to hypertension (Topol and Teirstein, 2016).

-Diabetes is a heterogenous disorder whereby the insulin hormone is impaired, which results on elevated levels of glucose. Patients that have diabetes have higher risk of organ damage if not controlled. ESP adds to a contributing factor of heart disease (Mcphee et al., 2000)

-Dyslipidemia is an abnormal high level of cholesterol; this increases the risk and chances of blocked coronary arteries.

-Lipid profile (mg/dL) is a profile of the level of total cholesterol. It is a blood test performed to obtain this information. This was an evaluation of the Total cholesterol, Low density lipoprotein, High density lipoprotein and triglycerides (Topol and Teirstein, 2016).

-New York Heart Association (NYHA) places patients in one of four categories based on how much they are limited during physical activity.

3.10.4 Clinical presentation

Acute coronary syndrome (ACS) - The reduction of coronary blood flow leads to a decline in oxygen demand, resulting in the development of ACS. The following are the traditional types of ACS:

-Unstable angina; Non ST elevation myocardial infarction and ST elevation myocardial infarction (Topol and Teirstein, 2016).

-Non ACS angina chest pain is termed chronic stable angina.

3.10.5 Lesion characteristics

Target vessel, this referred to which vessel had the lesion. The following is a list of the main coronary arteries involved with in-stent restenosis (Topol and Teirstein, 2016).

-Left main

-Left anterior descending artery

-Left circumflex

-Right coronary artery

-Bifurcation is when another branch comes off the main artery and also had involvement.

3.10.6 Procedural characteristics

The procedural characteristics looked at:

-Use of pre-dilatation balloons

-Number of stents used and if longer length stents were implanted

-The use of any form of imaging to size a vessel during the procedure, as we found that the use of imaging helped to reduce the rate of in-stent restenosis from other studies.

3.10.6.1 Coronary angiogram

The coronary angiogram is considered the most accurate way to measure the severity of coronary artery disease. Patients that present themselves again with clinical symptoms will have a repeat coronary angiogram to assess the stent patency.

The procedure is performed in the cardiac catheterization laboratory by a specialized Cardiologist and a team of cardiovascular nurses, a radiographer and a clinical technologist. The role of the clinical technologist is primarily to monitor the patient's vital signs, i.e. heart rate, rhythm and blood pressure. The patient's details and baseline measurements will be documented. If there is presence of in-stent stenosis, the Cardiologist will recommend the most suitable treatment option (Topol and Teirstein, 2016).

3.10.6.2 Percutaneous transluminal coronary angioplasty and stenting

Percutaneous transluminal coronary angioplasty and stenting are non-surgical techniques that are used to open blocked arteries as well blocked stents. Patients present with in-stent restenosis will either have intra-cardiac imaging to evaluate the severity as well as ballooning of the stent to re-establish flow (Topol and Teirstein, 2016).

The angiographic definition of In-stent restenosis was defined as stenosis within the stented segment or its edge (5 mm segment adjacent to the stent) of > 50% of the vessels diameters determined by coronary angiography (Her and Shin, 2018).

3.11 Statistical analysis

The collected data was analysed using the SPSS version 26.0 and Medcalc version 19.4.0. This SPSS version enabled the researcher to analyse the following parameters therefore it was perceived as befitting for this particular research study. Nonetheless, the collection data was recorded on a data collecting sheet and the means standard deviation will be used. By using the standard means of deviation this ensured that the collected data was entered on an excel page.

All data obtained from the questionnaires were depicted on spread-sheets. Descriptive statistics were presented as number and percentages. Bar charts were constructed to present findings of the study as a visual summary of results obtained from the data.

3.12 Ethical considerations

The permission to conduct the study was obtained from the Durban University of Technology and a letter requesting permission to conduct the study was sent to the gatekeeper, EThekwini Heart Hospital and Dr Gafoor and Dr Sooiwala Inc. The confidentiality and anonymity of participants was maintained at all times by means of allocating study numbers when data was logged in the spread-sheet. Additionally, there was no risk of patients' lives or treatment as this was a retrospective study evaluating the data collected, to let us know what may be the potential cause of in-stent restenosis.

The study was conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, the South African Guidelines of Good Clinical Practice (2006), The Medical Research Council (MRC) Ethical Guidelines for Research (2002) and the Department of Health Ethics in Health Research: Principles Processes and studies (2015). Patient details were known solely by the investigator

and stored in an electronic format with encryption. Encryption passwords were known only by the investigator.

The collected data material and documents related to the study and patient details, i.e., hard copies and electronic backups stored in a secure restricted lockable cupboard of which access can be obtained by the investigator only. All documents will be stored for a period of 5 years, thereafter disposed of appropriately, i.e., hard copies will be shredded, electronic backups deleted, and storage devices formatted.

CHAPTER 4: DATA FINDINGS AND DISCUSSION

4.1 Introduction

This chapter presents the results obtained from the research study. The data collected was analysed with SPSS version 26.0 and Medcalc version 19.4.0. The results are presented as descriptive statistics in the form of graphs, cross tabulations and other figures for the quantitative data that was collected.

4.2 The Sample

In total, the data of 57 patients was analysed.

4.3 Patient's gender findings

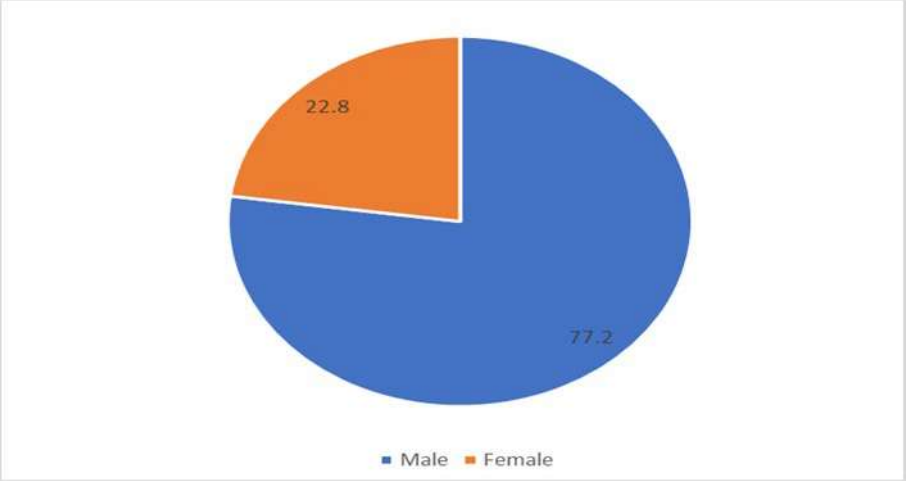

Figure 7: The gender ratio

Overall, the ratio of males to females is approximately 3:1 (77.2%: 22.8%) (p < 0.001), as displayed by the pie chart (Figure 7). It has been reported by previous studies that a higher risk of stenosis in male patients is present rather than in female patients (Jukema, 2011, Verschuren et al., 2011). This study shows a consistency with this finding.

4.4 Patient's race findings

Figure 8 displays the distribution of the patient's race for this study.

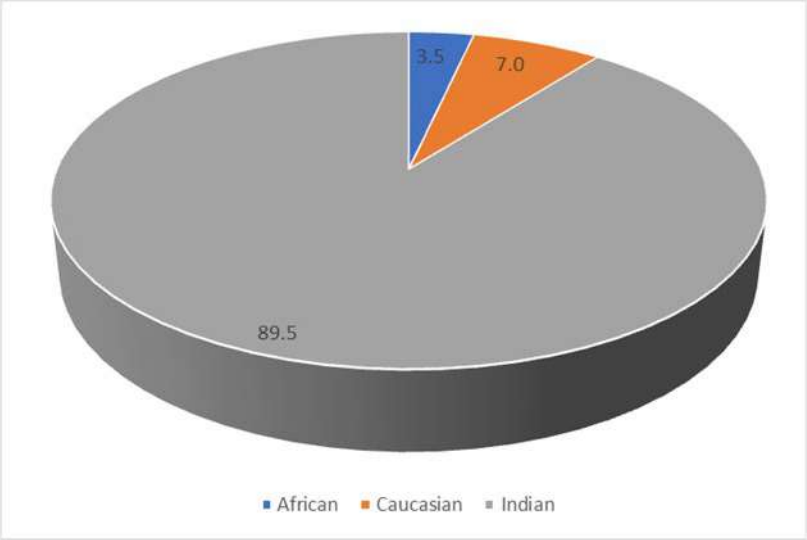

Figure 8: The race distribution.

Within the race category, 89.5% of patients were Indian, 7% of patients were Caucasian and 3.5% of patients were African.

Table 2 represents a cross tabulation of patient's race and gender.

Table 2: Cross-tabulation of patient's race and gender

		GENDER		Total
RACE		Male	Female	
African	Count	1	1	2
	% within RACE	50,0%	50,0%	100,0%
	% within GENDER	2,3%	7,7%	3,5%
	% of Total	1,8%	1,8%	3,5%
Caucasian	Count	2	2	4
	% within RACE	50,0%	50,0%	100,0%
	% within GENDER	4,5%	15,4%	7,0%
	% of Total	3,5%	3,5%	7,0%
Indian	Count	41	10	51
	% within RACE	80,4%	19,6%	100,0%
	% within GENDER	93,2%	76,9%	89,5%
	% of Total	71,9%	17,5%	89,5%
Total	Count	44	13	57
	% within RACE	77,2%	22,8%	100,0%
	% within GENDER	100,0%	100,0%	100,0%
	% of Total	77,2%	22,8%	100,0%
Fisher's Exact Test p-value = 0.144				

Africans- Out of our study of 57 patients, 2 were within the race category of African with one each being male and female. They represent 3.5% of all the data as well as 2.3% of males and 7.7% of females in this study.

Caucasian- Out of our study of 57 patients, 4 patients were in the race category of Caucasian with 2 each being male and female. This race group represents 7% of the patients within this study as well as 4.5% of males and 15.4% of females in this study.

Indian- Out of our study of 57 patients, 51 patients belonged to the race category of Indian. This race group represents the vast majority of this study and this may be due to the location of this hospital as we have a large Indian background in Durban as may be compared to other locations within this province. This race category represents 89.5% of the patients within this study as well as 93.2% of males and 76.9% of females in this study.

Total- This study consists of 44 males and 13 females, which result in our total of 57 patients. This study, therefore, consists of 77.2% males and 22.8% females. The males are largely represented by Indians (89.5%), followed by Caucasians (4.5%) and lastly Africans (2.3%). The females are also largely represented by Indians (76.9%), followed by Caucasians (15.4%) and lastly Africans (7.7%).

This study may be able to draw conclusions about the Indian race in Durban but unfortunately, due to its low numbers, may be unable to do so for the Caucasian and African races. The vast majority of patients in this study are therefore Indian males.

4.5 Patient's age distribution

Table 3 displays the minimum and maximum age of the patients in the study.

Table 3: The age distribution

N	Minimum	Maximum	Mean	Std. Deviation
57	39.00	81.00	61.21	10.35

The minimum age was 39 years, and the maximum age was 81 years. The mean age of the patient's was 61 years. The age of the patients are varied. The most common age was 59 patients with 6 patients (10.5%) from this age group. The relationship between age and restenosis is statistically the same and increased risk of restenosis with increasing age has not yet been demonstrated clearly.

4.6 Patient's history and risk factors

Table 4 and Figure 9 depict the patient's history, or as can be termed: the risk factors.

Table 4: Patient's history and risk factors

	No		Yes	
	Count	Row %	Count	Row %
Family History	34	59,6%	23	40,4%
Previous Surgery	47	100,0%	0	0,0%
Hypertension	11	19,3%	46	80,7%
Diabetes Mellitus	16	28,1%	41	71,9%
Dyslipidemia	12	21,1%	45	78,9%
Kidney Disease	44	89,8%	5	10,2%

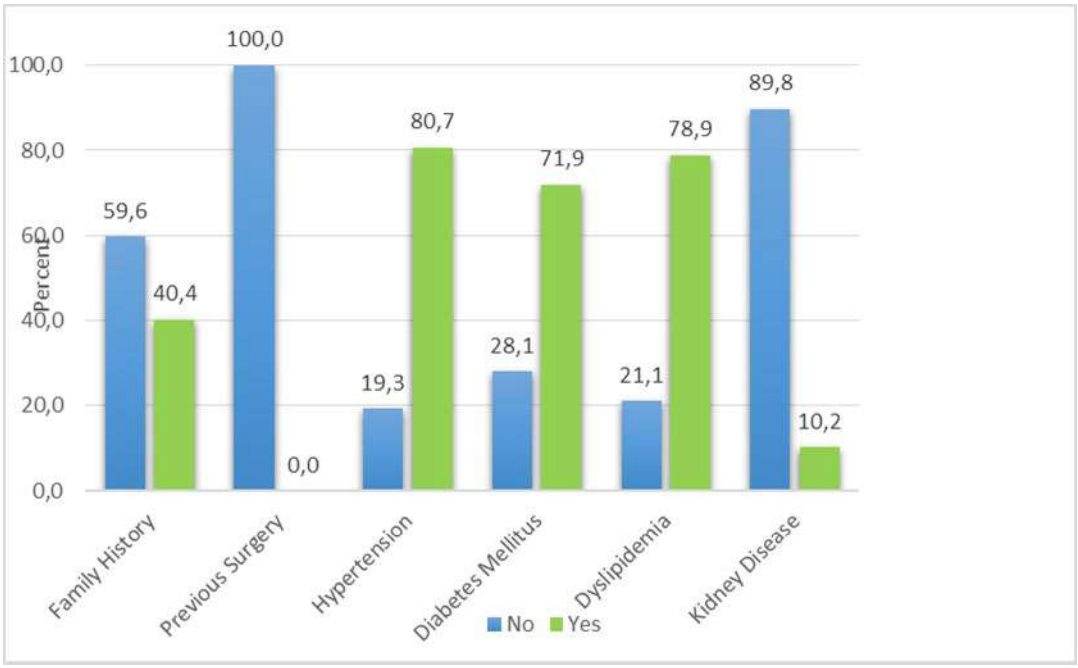

Figure 9: Patient's history and risk factors

Most patients (80.7%) also presented with hypertension and were under medical therapy for this. This was followed by dyslipidemia (78.9%) and thereafter diabetes mellitus (71.9%). Chances are these were found to be present concurrently with one another in most patients. Family history was found to be a factor in almost half of the patients (40.4%). One in ten patients had kidney disease which depicts that patient's kidney diseases had a poor prognosis with stent implantation.

Most studies reported a significant correlation between hypertension and in-stent restenosis. A meta- analysis of previous studies performed in 1995 showed that high blood pressure was significantly associated with in-stent restenosis (Sajadian 2018; Alizadeh et al., 2018).

4.7 Patient's tobacco use

There were almost as many smokers and ex-smokers, than those who hadn't smoked before. Therefore, there was no significance for smoking and ex-smokers in this study. This is displayed in Table 5.

Table 5: Patient's tobacco use

	No	Yes	Ex-smoker
Frequency	30	15	12
Percent	52,6	26,3	21,1

4.8 Clinical Parameters

Table 6: Descriptive statistics for the data of the cholesterol levels

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Initial Total Cholesterol	52	4,55	1,14	4,25	2,09	7,20
In-stent Total Cholesterol	56	4,27	1,13	4,15	2,40	8,00

The central measure for initial is higher than the in-stent value. The Wilcoxon test indicates that the difference is significant (p = 0.013). That is, the cholesterol levels are lower in the in-stent cases. This indicates that their cholesterol levels are being monitored and are well controlled under current therapy by their Cardiologist and follow up visits. This also indicates that the in-stent restenosis was not affected by the patient's cholesterol level and cholesterol control.

4.9 Clinical presentation

Acute coronary syndrome largely refers to a group of clinical symptoms or presentations, which includes: Unstable angina, NSTEMI and STEMI (Figure 10). Patients may therefore have myocardial ischemia or myocardial infarction.

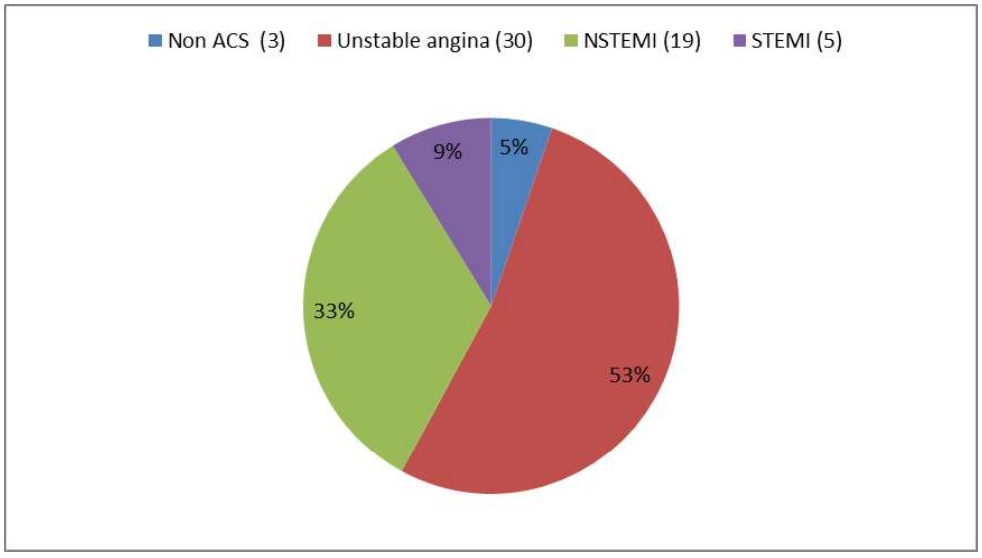

Figure 10: Clinical presentation

The clinical presentation shows that unstable angina was the most common presentation. Figure 10 shows 53% clinically presented with unstable angina. This is followed by those with NSTEMI, which accounts to 33% of those under study. Although other clinical factors were present, they accounted to less than 10% of patients under the study.

It is to be noted that 10 patients (17.54%) had positive exercise stress tests which then prompted the Cardiologist to perform a coronary angiography to evaluate stent patency. Coronary angiography then revealed in-stent restenosis. One of these 10 patients also developed symptoms as well as ECG changes on the treadmill. One patient had an inconclusive stress test but developed chest pain on the treadmill which prompted the Cardiologist to perform a coronary angiography. One other presentation that is of note is that 7 patients presented for their follow up appointment with angina equivalent of dyspnea. This also prompted the Cardiologist to investigate further and perform a coronary angiogram. In all these cases, the Cardiologist confirmed ISR. This emphasises how important follow up appointments are post percutaneous coronary interventions.

4.10 INITIAL PROCEDURE

4.10.1 Vessels affected by ISR

Table 7 displays the vessels which had in-stent restenosis.

Table 7: In-stent restenosis vessels

INSTENT STENOSIS VESSEL					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	RSV	1	1,8	1,8	1,8
	RCA	12	21,1	21,1	22,8
	OM	1	1,8	1,8	24,6
	LMS	1	1,8	1,8	26,3
	LCX	9	15,8	15,8	42,1
	LAD	32	56,1	56,1	98,2
	HIG	1	1,8	1,8	100,0
	Total	57	100,0	100,0	

This shows that the most common vessel with in-stent restenosis was the LAD which accounts to more than half of the patients in this study, 32 patients (56.1%). This is followed by 12 patients with in-stent stenosis of the RCA, which accounts to 21.1% of this study. 9 patients had in-stent stenosis of the LCx, as well as 2 patients with ISR of the OM, one of it being the high OM. The LMS was one of the least common vessels with ISR, with there being only one patient that presented with ISR of the

LMS (Figure 11). This patient was then sent for CABG due to the nature of the vessel.

Studies have shown that in-stent restenosis is more common in left anterior descending artery in distal or proximal lesions (Sajadian 2018; Alizadeh et al., 2018).

Figure 11 below clearly displays the spread of vessels with ISR.

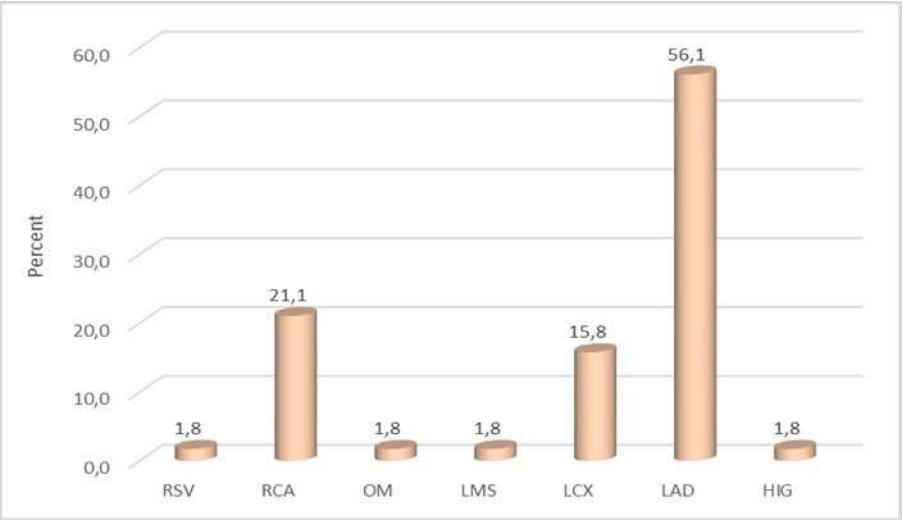

Figure 11: In-stent restenosis vessels

4.10.2 Use of stent during initial procedure

Figure 12 displays the stents used in the initial procedure for the patient.

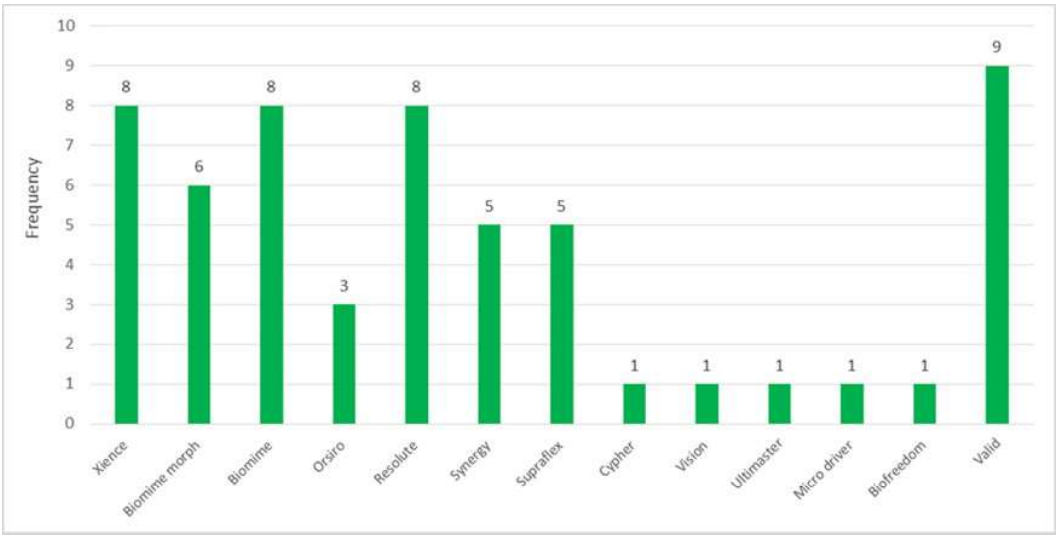

Figure 12: Stents used during initial procedure

There were 9 patients whose information was lacking due to their initial procedure being with other Cardiologists/hospitals, or their procedure being too long ago that the data was not available even at their previous Cardiologist.

The most common stents used were Xience, Biomime and Resolute. These were used for 8 patients each, accounting to almost half of the patients that were part of this study. This is followed by the use of Biomime Morph for 6 patients. Biomime Morph stents are known to be longer length stents used for longer length lesions. Synergy and Supraflex were used for 5 patients each.

Figure 12 shows that there is a varied use of stents across most companies.

4.10.3 Drug coating on stents

Figure 13 shows the distribution of drug coating on the stents.

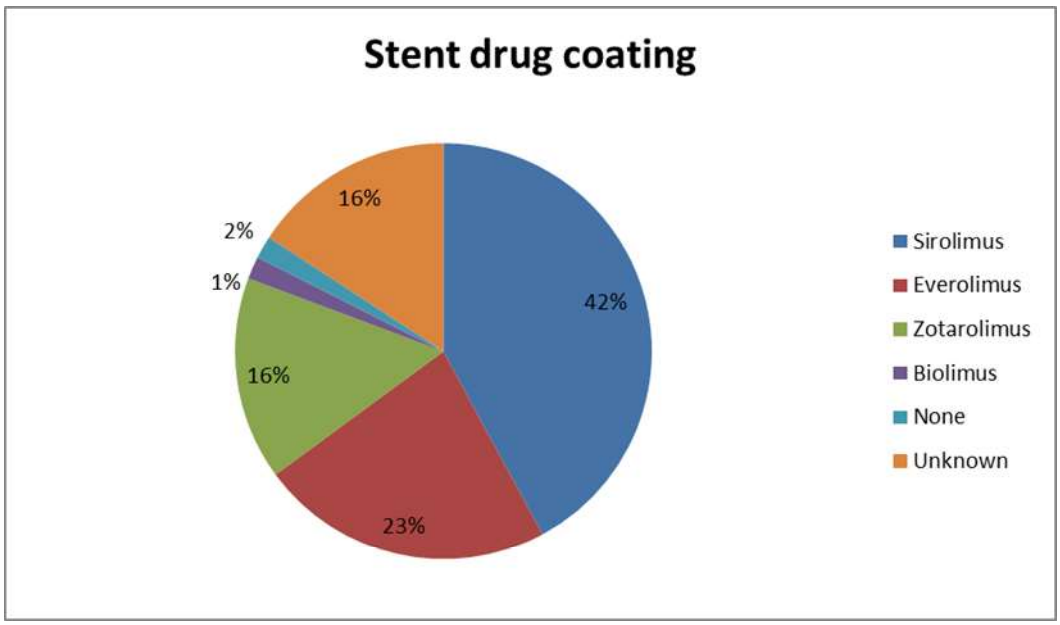

Figure 13: Stent drug coating

-Sirolimus: This drug coating is found on the following stents: Biomime, Biomime Morph, Supraflex, Orsiro, Ultimaster and Cypher. This represents almost half of the patients in this study, and accounts to 42% of patients.

-Everolimus: This drug coating is found on the following stents: Synergy and Xience. This represents 23% of patients in this study.

-Zotarolimus: This drug coating is found on the following stents: Resolute and Microdriver. This represents 16% of patients in this study.

-Biolimus: This drug is only found on the Biofreedom range of stents and was only used once for one patient.

One patient was treated with a bare metal stent, the Vision stent. This was done at a governmental institution in 2009. Drug eluting stents were not as prevalent back

then. 9 patients (16%) had data missing, therefore, it is unknown which stent or stent drug coating was in use for the initial procedure.

4.10.4 Stent diameter and length

Table 8 is a measurement of the stent diameter used.

Table 8: Stent diameter

STENT DIAMETER (mm)	FREQUENCY
2.25	8
2.50	15
2.75	19
3.0	14
3.25	0
3.50	9
TOTAL	65

It is to be noted that the frequency of stents used is higher than the number of patients in this study as some vessels have more than one stent. This contributes to overlapping stents and the need for this is judged by the Cardiologist at the time of PCI. Another reason for this may also be the need to PCI different segments of a vessel such as mid-vessel and proximal vessel and since the diameter of the vessels may be different, different stents are used to avoid stepdown of the vessel. The maximum number of stents that was used in a single vessel in this study is 3.

Table 9 provides us with the length of stent used in a vessel.

Table 9: Stent length

STENT LENGTH (mm)	FREQUENCY	Percentage (%)
<20	11	19.3
20-30	12	21.1
31-40	9	15.8
41-50	4	7.0
51-60	7	12.3
61-70	3	5.3
71-80	3	5.3
81-90	-	0.0
91-100	-	0.0
101-110	1	1.7
MISSING	7	12.2
TOTAL	57	100.0

The length given is the total cumulative length of the stented vessel, this may or may not include more than one stent used in the vessel of interest. The information for 7 patients is missing due to the initial procedure being done by a different doctor and hospital and this information was not available to this practise. The minimum stent length was <20 mm. The maximum stent length was between 101-110 mm, and this indicates that multiple stents were used, overlapping one another.

The most frequent stent length of the vessel was between 20-30 mm and this was 21% of the patients. This stent length was used in 12 cases. This was followed by 11 cases with the stent length below 20 mm. Most of the patients had a stent length below 40 mm, although there were some varied and longer stents used.

4.10.5 Use of pre-dilation and post-dilation balloon

A pre-dilation balloon is used before the implantation of a stent in order to prepare the vessel for stent implantation. A pre-dilation balloon is a semi-compliant balloon

inflated in a vessel to a certain pressure as chosen by the Cardiologist, and will expand the vessel in order to facilitate ease of stent deliverability and flexibility of the vessel. It is a softer, more compliant balloon that will take the shape of the vessel and prepare the walls to accommodate a stent.

Table 10: Use of pre-dilation balloon

USE OF PRE-DILATION BALLOON					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	10	17,5	21,3	21,3
	Yes	37	64,9	78,7	100,0
	Total	47	82,5	100,0	
Missing	System	10	17,5		
Total		57	100,0		

In this study, 37 patients had their ISR vessel expanded with a pre-dilation balloon before the initial stent implantation (Table 10). This accounts to 64.9% of patients in this study. 10 patients did not have the use of a pre-dilation balloon before stent delivery. This may be due to various reasons, as it has been noted that the initial procedure may have been done by different Cardiologists in different hospitals. It is also to be noted that although a pre-dilation balloon can be used before stent implantation, it is not always the case. It is operator and lesion dependent. Information for 10 patients are missing so it is unknown whether their vessels were prepared by a pre-dilation balloon or not.

A post-dilation balloon is used after the implantation of a stent. This is usually a non-compliant balloon that is inflated to a certain pressure as chosen by the Cardiologist, in order to ensure proper apposition of a stent against the vessel wall. It keeps its shape and pushes out the frame structure of a stent in order to fix it against the vessel wall firmly.

Table 11: Use of post-dilation balloon

USE OF POST-DILATION BALLOON					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	14	24,6	30,4	30,4
	Yes	32	56,1	69,6	100,0
	Total	46	80,7	100,0	
Missing	System	11	19,3		
Total		57	100,0		

In this study, 32 patients had their initial stent post dilated with a post-dilation balloon. This accounts to 56.1% of patients in this study (Table 11). 14 patients did not have the use of a post-dilation balloon following stent implantation. This may be due to various reasons and once again, is operator and lesion dependent. Some Cardiologists may not see the need to post dilate if they feel that they have already achieved a satisfactory result. The information for 11 patients is missing so it is unknown whether they did have their vessel post dilated after stent implantation.

4.10.6 Complications

Table 12 shows that of the 47 patients who responded; nearly 9 out of 10 did not report any complications ($p < 0.001$). This accounts to 89.4% of the patients.

Table 12: Initial procedure complications

	Frequency	Percent
ACUTE STENT THROMBOSIS	1	2.1
ASYSTOLE/CLOT	1	2.1
ATRIAL FIBRILLATION	1	2.1
EMBOLIZATION TO LCX TERMINAL BRANCH	1	2.1
NONE	42	89.4
REACTION TO DYE	1	2.1
TOTAL	47	100.0

Of the complications that were noted, cardiac arrest and death were not present, which is a good indicator of the overall outcome of the procedure. Reaction to the dye, asystole, atrial fibrillation, acute stent thrombosis and embolism to the terminal branch of the LCx were the only complications reported.

The remaining 10 patients were from outer hospitals; therefore, their data was incomplete and unknown.

4.11 IN-STENT PROCEDURE

4.11.1 Time frame of procedures

The time frame for the in-stent restenosis procedure ranges from June 2018 to February 2020. These are all procedures that were done by this practise, by the Cardiologists, Dr Gafoor and Dr Soosiwala. The details for these procedures were found from patient's files.

4.11.2 Vessel characteristics

Several lesion characteristics have been shown to increase restenotic risk as shown in Table 13. The lesion-related factor most associated with in-stent restenosis has shown to be the length of lesion. Other factors include under expansion of the stents as well as overlapping stents.

Table 13: Vessel characteristics of the study group

Chronic total occlusion	2
Bifurcation stenting	1
Calcium in vessel	5
Overlapping stents	8
Under expansion of stents	12
Insegment stenosis	12
Intimal hyperplasia	3

Other factors that have related to the PCI procedure are multiple stents, stent fracture as well as the fact that IVUS was not used for guidance in the initial stent implantation. Multiple stents implanted during PCI is related to increased risk of ISR and the rationale relates to the longer lesion length or larger surface area covered by stent material. This may also contribute to insegment stenosis. Another factor, related to the procedure, is the use of IVUS to guide stent implantation.

IVUS guidance assists with correctly measuring the diameter, length and characteristics of a vessel. It is unknown whether IVUS may or may not have been used initially, this information was not available. In the in-stent restenosis procedure, it is with the help of IVUS that we are able to confirm stent under-expansion which accounted for ISR in 12 patients in this study (Figure 11). It is also to be noted that IVUS was not used in all of the in-stent restenosis procedures, it was only used

when deemed necessary by the Cardiologist in order to investigate the vessel or stent further.

Insegment stenosis occurs when a region within the stent and outside of the stent has a degree of stenosis. This may be on the proximal or distal end of the stent. This occurred for 12 patients in this study (Table 13).

It was found that 8 patients with overlapping stents presented with ISR. This may also indicate the presence of longer lesion lengths as well. Overlapping stents may also be present due to incorrect size of stents available; therefore more than one stent needs to be used to adequately cover the lesion.

Calcium may form in a vessel and this makes it difficult to adequately expand a stent. 5 patients were found to have calcium develop in the vessel which was causing narrowing. Repeat inflation does not necessary yield good results unless the calcium is soft and pliable.

Intimal hyperplasia may develop causing obstruction in a vessel. This was found to be the case in 3 patients. It was identified with the guidance of IVUS and is usually termed soft plaque.

4.11.3 Use of drug eluting balloon

Table 14 gives insight as to the use of a drug eluting balloon in order to address in-stent restenosis of the vessel.

Table 14: Drug eluting balloons used with drug coating

DRUG ELUTING BALLOON USED	DRUG COATING ON BALLOON	FREQUENCY OF USE
Eurocor Dior	Paclitaxel	15
MagicTouch	Sirolimus	5
Sequent Please	Paclitaxel	10
TOTAL		30

30 patients out of 57 patients (52.6%) were treated with the use of drug eluting balloons. This type of balloon may be used for in-stent as well as insegment restenosis.

At the time of the procedure, there were only 3 types available with varying sizes. The three companies used by the Cardiologist were Eurocor Dior, MagicTouch and Sequent Please. The drug coatings on the balloons were paclitaxel and Sirolimus. Most commonly, Eurocor Dior was used followed by Sequent Please. Sizing of the balloon was dependant on the vessel and inflation time is normally 60 seconds. The most common drug coating on the drug eluting balloons used was Paclitaxel, followed by sirolimus which is a drug coating that is still used on stents.

4.11.4 Use of stent

Tables 15 and 16 display the use of stents in order to address in-stent restenosis.

Table 15: Use of stent in ISR procedure

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	46	80,7	82,1	82,1
	Yes	10	17,5	17,9	100,0
	Total	56	98,2	100,0	
Missing	System	1	1,8		
Total		57	100,0		

Table 16: Stent drug coating

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Missing	47	82,5	82,5	82,5
	EVEROLIMUS	7	12,3	12,3	94,7
	SIROLIMUS	2	3,5	3,5	98,2
	ZOTAROLIMUS	1	1,8	1,8	100,0
	Total	57	100,0	100,0	

10 patients out of 57 patients (17.5%) were stented in order to address the in-stent restenosis that resulted in the vessel. The most common drug coating on the stent is Everolimus, which was present for 7 out of 10 of the stented patients.

There were remaining 17 patients who had in-stent stenosis but were not treated with a drug eluting balloon or a stent. The reason for this may be that the Cardiologist decided that CABG would provide a better outcome for the patient, or that the disease within the stent was not functionally significant. Another treatment that the Cardiologist may have opted for is medical therapy.

4.11.5 History of In-stent restenosis

Table 17 illustrates the patients who have had a prior history of in-stent restenosis.

Table 17: History of in-stent restenosis

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	5	8,8	9,3	9,3
	Yes	19	33,3	35,2	44,4
	None	30	52,6	55,6	100,0
	Total	54	94,7	100,0	
Missing	System	3	5,3		
Total		57	100,0		

19 patients out of 57 patients (33.3%) presented with in-stent restenosis more than one time. This reflects one third of the patients that were part of our study.

Of these patients, 15 were reported to have unstable angina. This means that 78.9% of patients who presented with repeat in-stent restenosis were patients with unstable angina.

15 patients with repeat in-stent restenosis were also found to be male.

5 patients out of 19 patients (26.3%) had overlapping stents put in initially. Only 3 patients with overlapping stents presented with in-stent restenosis for the first time during this study. Overlapping stents are usually for longer length lesions. In some

cases, longer length lesions were also dealt with longer length stents known as Biomime Morph. These stents are known to have length above 40 mm, up to and including 60 mm. These stents resulted in repeat in-stent restenosis, a total of 2 out of 5 times.

The most common stent used resulting in repeat in-stent restenosis was Biomime. Biomime stents were reported to have been used initially for a total of 8 patients, although it had been identified as having multiple in-stent restenosis for 6 of those patients. In this study, the risk of repeat in-stent restenosis with a Biomime stent is, therefore, 75%.

The vessel with the highest history of in-stent restenosis in this study is the right coronary artery. This is closely followed by the left anterior descending artery.

Following repeat in-stent restenosis, most patients were then referred for surgery as they were not doing well with stents. Some were referred for medical therapy to address symptoms as the lesions were found to be non-significant. The time frame for these patients do vary, with the initial procedure being done at least more than 3 years ago, and the oldest being stented 19 years ago. The operator for the initial as well as repeat in-stent stenosis varies, with some this data was unknown, as this may have also been before their referral to this practise. However, the final in-stent restenosis documented during this study was done by the Cardiologists of this practise. Therefore, no conclusion can be derived with regards to the operator of the case and situation of the case at that time that could have resulted in certain patients having repeated in-stent restenosis.

4.11.6 Complications for ISR procedure

The complications listed in Table 18 are an indication of the success of the in-stent procedure.

Table 18: Procedural complications

PROCEDURAL COMPLICATIONS					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Missing	4	7,0	7,0	7,0
	3 VESSEL DISEASE. IABP INSERTED	1	1,8	1,8	8,8
	CLOT IN THE LM/LAD/LCX. CARDIAC ARREST. TPM. DEATH	1	1,8	1,8	10,5
	GRADE V THROMBUS FOUND. ASPIRATION CATHETER USED, CLOT PROPAGATED CAUSING	1	1,8	1,8	12,3
	NONE	46	80,7	80,7	93,0
	NONE. SUCCESSFUL RECANULISATION OF CTO OF MID RCA (DISTAL PART OF STENT)	1	1,8	1,8	94,7
	PT DEVELOPED SEVERE BRADYCARDIA. TPM INSERTED + ATROPINE GIVEN	1	1,8	1,8	96,5
	SATISFACTORY BUT SUBOPTIMAL POBA	1	1,8	1,8	98,2
	UNABLE TO PASS GUIDEWIRE BEYOND PROXIMAL STENT. FURTHER INTERVENTION WAS AE	1	1,8	1,8	100,0
	Total	57	100,0	100,0	

47 patients were reported to have no complications, indicating successful procedures in 82.5% of the cases. 1 patient was reported to have had a satisfactory result. 1 case was abandoned due to the vessel characteristics not being able to allow a guidewire to pass through.

Clot was found in 2 patients. These clots propagated causing the heart rate and blood pressure to drop. This caused cardiac arrest and despite the use of a temporary pacemaker, it resulted in death of one of the patients.

One patient required an Intra-aortic Balloon Pump to be inserted due to severe disease and poor prognosis.

The temporary pacemaker was inserted for 3 patients. This was due to bradycardia as well as asystole.

There was one patient whose procedure ended with death. Unfortunately, everything possible was done for her but it was not enough. She was no stranger to in-stent restenosis and with resulting calcium in the vessel; she was undergoing lithotripsy, a shockwave therapy similar to that used for kidney stones. This patient also

presented with in-stent restenosis 6 times previously as well and despite CABG, her myocardial perfusion remained subpar.

4.11.7 Patient characteristics

Patient characteristics of the study group are represented in Table 19 below.

Table 19: Patient characteristics of the study group

Late stent thrombosis	1
Acute stent thrombosis	3
Undersized	1
Referred for CABG	12
Defaulted clopiwin plus	1
Lithotripsy to calcium (shockwave)	1
Referred for medical management	3
Non- compliant with medication	2

Acute and late stent thrombosis was still found to be a factor for 4 patients in this study, with acute stent thrombosis occurring for 3 patients (Table 19). They were in need of a repeat procedure within 30 days of their initial PCI.

12 patients from this study were referred for CABG following in-stent restenosis. Most of them presented with a history of ISR. Some of them were referred for CABG as the Cardiologist believed it to be the best long term option for them, especially if they were not doing well with stents. 21% of patients were thus found to be better suited and will have better long-term outcomes with CABG rather than PCI. This is due to the lesion characteristics as well as vessel characteristics of the patient.

3 patients were referred for medical therapy as their lesion was not significant enough to warrant intervention. The Cardiologist preferred not to cause any disruption or interfere with a vessel if it was not necessary.

3 patients were not compliant with medication, one of them defaulting clopiwin plus which is necessary post PCI. This resulted in inadequate care of the stented area and resulted in ISR.

One patient with ISR underwent lithotripsy to calcium (shockwave therapy). This procedure was disrupted by clot spreading to her native vessels, resulting in cardiac arrest and death. This was the patient's seventh procedure for ISR. Even having undergone CABG to better perfuse her arteries, stents and CABG were not providing a suitable outcome for her.

CHAPTER 5: DISCUSSION

5.1 Introduction

In-stent restenosis represents approximately 10% of all PCI and is treated most commonly with another stent (Moussa et al., 2020). A multitude of trials and studies have been performed to get a better understanding of in-stent restenosis. These studies have shown three major categories: Patient predictors, Vessel predictors and Procedural factors. Identifying risk factors for the development of restenosis is helpful for patient risk stratification. An improved understanding of the processes of restenosis could lead to its prevention, saving patients from undergoing further procedures and reducing costs for society.

In this study, risk factors of ISR after PCI were screened from baseline data, coronary lesion related factors and stent related factors.

5.2 Patient factors

A review article showed in-stent restenosis is more likely to be found in female than male (Gurlek et al., 1995). This is inconsistent with this study, which indicated a higher prevalence of in-stent restenosis amongst Indian males. This can be argued to suggest that this might have been attributed to the higher number of males' within the Durban area.

In the past, diabetes mellitus has shown to be a high risk predictor of in-stent restenosis with bare mental stents. With the evolution drug eluting stents this number has been reduced compared to bare metal stents, but there is still an increase of incidence of restenosis in diabetic patients over the non-diabetic patients. There are many factors that could contribute to these patients having in-stent restenosis as patients with diabetes generally have smaller calibre vessels and longer length lesions. Studies show that there is a higher risk of in-stent restenosis in patients with longer lesions and small vessels. So regardless of diabetes, these factors also contribute to the incidence of in-stent restenosis. Diabetic patients remain at risk for incidence of in-stent restenosis despite the use of drug eluting stents (Jukema 2011;

Verschuren et al., 2011). Two thirds of the patients in this study presented with diabetes.

Hypertension and dyslipidemia had a high number of patients that presented with in-stent restenosis and this could be due to endothelial dysfunction in hypertension, dyslipidemia and in-stent restenosis. From the analysis of the cholesterol parameters, it appears that the cholesterol levels did not increase. This could be due to good and proper medical therapy as well as patients being compliant. Cholesterol levels did not show any difference or contribution to the increased rate of in-stent restenosis.

There were similar numbers of patients who were smokers and ex-smokers, but these are nearly half (each) of never smoked. Smoking causes cell proliferation and this increases the risk of in-stent restenosis. Some studies have shown smoking to be an independent risk factor to predict restenosis, however, other studies showed that smoking does not increase the risk of restenosis (Sajadian 2018; Alizadeh et al., 2018).

Even though the treatment method for in-stent restenosis is to use a second stent, a concern that may arise are issues of late stent thrombosis and very late thrombosis. The predominant etiology of late stent thrombosis and very late stent thrombosis revolves around the observation of delayed endothelialisation (Kim and Dean, 2011). The research study show that a total of three participants presented with late and very late stent thrombosis. The theory and explanation behind this could be that there are both chemical and anatomical factors, more concentrated and localised anti-proliferative drug dose, double layer of non resorbable polymer acting as a substrate of thrombosis, predisposition of suboptimal stent expansion in the area of stent overlap resulting in a smaller post deployment.

The wide spread adoption of DES for small arteries, long lesions, complex coronary lesions, diabetes, and a history of bypass surgery has been the trigger of a significant number of patients re-presenting with DES restenosis in contemporary clinical practice (Her and Shin, 2018). Although the consensus is to use a DES, it may not be appropriate for all clinical settings.

5.3 Vessel factors

Stent implantation of the left anterior descending artery showed a higher predisposition towards in-stent restenosis as compared to the other arteries.

The results of the study indicates that the longer the length of the stent the higher the rate of in-stent restenosis. The diameter and lesion length also independently impact the predictive incidence of in-stent restenosis. The larger diameter and shorter lesions demonstrate significantly lower restenosis rates. It appears the length of the stent has repeatedly been identified as an independent predictor of in-stent restenosis (Jukema, 2011; Verschuren et al., 2011)

Diabetic patients have smaller calibre vessels with lengthy lesions and the disease is generally more diffuse compared to non-diabetic patients and this makes the first intervention more difficult and challenging in choosing the appropriate stent length to cover the diseased segment (Jukema, 2011; Verschuren et al., 2011). It has been found that using angiography alone can cause geographical miss when landing the stent and this predisposes the patient to the development of edge restenosis. The role of intravascular imaging and optical coherence tomography will help overcome these issues in the future (Paramasivam 2019; Devasia et al., 2019).

It appears that even though first generation stents have been improved on over the years on the stent design from thicker struts to thinner struts, we are still faced with in-stent restenosis (Her and Shin; 2018).

Another study showed that stent length, stent diameter and the number of stents were important factors associated with poor survival outcome. The longer length was a predictor of stent thrombosis and mortality (Duggal et al., 2018).

5.4 Procedural factors

Factors that do influence the success of stent implantation are the type of stent, the skills of the Cardiologist and if the lesion was prepared adequately. Also the use of intravascular ultrasound imaging in sizing of the vessel has shown to give better results in placement of stents. The study has found that the vessels were prepared adequately by the operator. All vessels were ballooned before stenting, as well as

post dilated, ensuring that the stent was adequately placed against the vessel wall and fully patent and apposed.

The type of DES (first and second generation DES stents) could not be compared because 10 out of the 52 patients had undergone PCI at a different hospital and were presented to this practise for the first time with DES- ISR.

Additionally, in South Africa we have a variety of stent types with various combinations of polymers and anti- proliferative drugs that make it difficult to segregate them into groups.

Therefore, knowing these factors and their contribution towards in-stent restenosis is useful in risk stratification of patients and to the understanding of complexed disease, as well as, tailored therapy and treatment modalities.

The in-stent restenosis rates observed in this study was consistent with the literature published. Nonetheless, the low statistical sample size is always one of the possible reasons for the failure to find significant relationships among variables.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

Restenosis is an independent predictor for mortality with other relevant clinical factors like diabetes mellitus, sex, age and previous surgery. These types of patients require routine follow up and intense medical management to reduce the rate of in-stent restenosis.

An improved understanding of the processes of restenosis could lead to its prevention, saving patients from undergoing further procedures and reducing cost for society.

This study shows that there are factors that affect patients with stents and cause in-stent restenosis. This has been an on-going problem in the field of interventional cardiology even with improvement of stents from baremetal to drug eluting stents.

Drug eluting stents have changed and improved in-stent restenosis drastically but it has not eradicated the problem. Stents over the years have improved on deliverability as well as stent design and pharmacologic therapy, but further improvement will be needed. Regardless of the stent type, small vessel size and stent length are the most important predictors of in-stent restenosis.

Despite stent improvement the overall rate of in-stent restenosis remains relatively high.

This study suffers the obvious limitations inherent to observational nonrandomized registries. Analysis of outcomes was not performed on treatment strategy due to the stent choice and treatment strategy was based on the operator's discretion. The study only focused on one area of interest. Thus the findings cannot be generalised to the whole population.

The use of IVUS and OCT guidance will assist with correct sizing of vessels, stent deployment and stent apposition and this will reduce the number of in-stent restenosis caused by procedural factors.

Drug coated balloons is currently the first choice treatment for restenosis or stent-in-stent deployment, but with a drug coated balloon avoids another layer of metal struts

on a pre-existing stent. The ideal treatment for in-stent restenosis remains an area of active investigation that is in constant evolution.

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APPENDICES

8.1 Appendix A- Parameters collected

DEMOGRAPHICS

AGE: _____

GENDER: _____

RACE: _____

PATIENT RISK FACTORS

FAMILY HISTORY	YES ☐	NO ☐	
PREVIOUS SURGERY	YES ☐	NO ☐	IF YES, SPECIFY: _____
HYPERTENSION	YES ☐	NO ☐	
DIABETES MELLITUS	YES ☐	NO ☐	
DYSLIPIDEMIA	YES ☐	NO ☐	
KIDNEY DISEASE	YES ☐	NO ☐	
TOBACCO USE	YES ☐	NO ☐	PREVIOUS USE ☐

BLOOD PARAMETERS

INITIAL TOTAL CHOLESTEROL _____

INSTENT TOTAL CHOLESTEROL _____

CLINICAL PRESENTATION

ACS	YES ☐	NO ☐	
NON-ACS	YES ☐	NO ☐	
UNSTABLE ANGINA	YES ☐	NO ☐	
MYOCARDIAL INFARCTION	YES ☐	NO ☐	
IF YES, SPECIFY	NSTEMI ☐		STEMI ☐
SILENT ISCHEMIA	YES ☐	NO ☐	
CLINICAL DIAGNOSIS	YES ☐	NO ☐	
	☐		☐

IF YES, SPECIFY POSITIVE STRESS TEST OTHER

IF OTHER, SPECIFY _____

LESION CHARACTERISTICS OF INSTENT RESTENOSIS VESSEL

VESSEL: _____

DETAILS OF INSTENT RESTENOSIS ……

……

……

……

INITIAL PROCEDURE DETAILS

DATE OF INITIAL PROCEDURE: _____

STENT USED: _____

STENT DETAILS:

NO OF STENTS USED: ☐

STENT 1: STENT DIAMETER _____

STENT LENGTH _____

STENT POSITION _____

STENT TYPE: BARE METAL ☐ DRUG ELUTING ☐

STENT DRUG COATING: EVEROLIMUS ☐ SIROLIMUS ☐

ZOTAROLIMUS ☐ OTHER ☐ _____

STENT 2: STENT DIAMETER _____

STENT LENGTH _____

STENT POSITION _____

STENT TYPE: BARE METAL ☐ DRUG ELUTING ☐

STENT DRUG COATING: EVEROLIMUS ☐ SIROLIMUS ☐

ZOTAROLIMUS ☐ OTHER ☐ _____

STENT 3: STENT DIAMETER _____

STENT LENGTH _____

STENT POSITION _____

STENT TYPE: BARE METAL ☐ DRUG ELUTING ☐

STENT DRUG COATING: EVEROLIMUS ☐ SIROLIMUS ☐

ZOTAROLIMUS ☐ OTHER ☐ _____

USE OF PREDILATION BALLOON YES ☐ NO ☐

IF YES, SPECIFY _____

USE OF POSTDILATION BALLOON YES ☐ NO ☐

IF YES, SPECIFY _____

PROCEDURAL COMPLICATIONS: …….

…….

…….

…….

…….

INSTENT RESTENOSIS PROCEDURE DETAILS

DATE OF INSTENT PROCEDURE: _____

INSTENT RESTENOSIS VESSEL: _____

LESION PARAMETERS:

OVERLAPPING STENTS ☐ INSEGMENT STENOSIS ☐

THROMBUS ☐ CALCIUM ☐

DETAILS IF NECESSARY: …….

…….

…….

…….

…….

USE OF IVUS TO ASSESS VESSEL ☐

IVUS FINDINGS: ……

……

……

……

……

USE OF DRUG ELUTING BALLOON YES ☐ NO ☐

IF YES, SPECIFY _____

BALLOON DRUG COATING _____

USE OF STENT: YES ☐ NO ☐

IF YES, SPECIFY:

STENT 1: STENT DIAMETER _____

STENT LENGTH _____

STENT POSITION _____

STENT TYPE: BARE METAL ☐ DRUG ELUTING ☐

STENT DRUG COATING: EVEROLIMUS ☐ SIROLIMUS ☐

ZOTAROLIMUS ☐ OTHER ☐ _____

STENT 2: STENT DIAMETER _____

STENT LENGTH _____

STENT POSITION _____

STENT TYPE: BARE METAL ☐ DRUG ELUTING ☐

STENT DRUG COATING: EVEROLIMUS ☐ SIROLIMUS ☐

ZOTAROLIMUS ☐ OTHER ☐ _____

HISTORY OF INSTENT RESTENOSIS YES ☐ NO ☐

IF YES, _____ TIMES

PROCEDURAL COMPLICATIONS: ……

……

……

……

……

OTHER CRITERIA: ……

……

……

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……