A Review On: Coronaray Artery Diseases

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Abstract- *Coronary artery disease (CAD) is the most dangerous heart disease which may lead to sudden cardiac death. Coronary artery disease (CAD) is the single most common cause of death in the developed world, responsible for about 1 in every 5 deaths.However, CAD diagnoses are quite expensive and time-consuming procedures which a patient need to go through. Diagnosis of CAD include ECG, Exercise Stress Test, Eco cardiogram, Radio Nuclide Imaging, Angiography etc. The eradication and management of CAD has been established through extensive studies and trials. Cholesterol modifying medication, Aspirin, B- blockers, Nitro-glycerine, Angiotensin converting Enzyme are some of the few therapeutic agents used for the relief of CAD.Managements of CAD patients include lifestyle modification, control of CAD risk factors, pharmacologic therapy, and patient education.This comprehensive review highlights brief about CAD.*

Keywords- Coronary artery disease, Stent, Vessels, Atherosclerosis, Plaque.

I. INTRODUCTION

Coronary artery disease (CAD), also called heart disease or ischemic heart disease, results from a complex process known as atherosclerosis (commonly called "hardening of the arteries"). In atherosclerosis, fatty deposits (plaques) of cholesterol and other cellular waste products build up in the inner linings of the heart's arteries.

II. TYPES OF CORONARY ARTERY DISEASES

A) Obstructive coronary artery disease

We treat narrowed or blocked vessels with lifestyle changes, medications, percutaneous coronary intervention, and/or surgery. Hybrid coronary revascularization is another option we offer for people with obstructive coronary artery disease.

B) Non- Obstructive coronary artery disease

People can have chest pain (angina) even when there are no narrowed or blocked vessels. We are one of the few centres in the United States specializing in the diagnosis and treatment of non-obstructive coronary artery disease.

C) Spontaneous- coronary artery dissection

Splitting of the layers of the coronary artery can lead to a unique type of heart attack that is often unrecognized. If not appropriately diagnosed, patients can become worse. We bring a personalized approach to the management of SCAD and have ongoing research to better understand this disease.

III. EPIDEMIOLOGY

Coronary heart disease is now the leading cause of death worldwide. An estimated 3.8 million men and 3.4 million women die each year from CHD.In developed countries heart disease is the leading cause of death in men and women. In Europe CHD accounts for an estimated 1.95 million deaths each year.CHD is the most common cause of deaths in the UK. An estimated 1 in 5 men and 1 in 6 women die from the disease each year.In 2003 CHD caused around 114,000 deaths in the UK.CHD is responsible for 110,000 deaths in England each year. More than 1.4 million suffer from angina and 275,000 people have a heart attack annually.

Death rates from CHD have been falling in the UK since the late 1970s. For people <65 years, they have fallen by 44% in the last ten years. A recent study has suggested that 58% of decline in CHD during the 1980s and 1990s was attributable to reduction in major risk factors, principally smoking. Treatments to individual, including secondary prevention explained the remaining decline in mortality.However despite recent declines the UK has a relatively high death rate from CHD. Among more developed countries only Ireland and Finland have a higher rate than the UK.Death rates from CHD are highest in Scotland and Northern England. The premature death rate for men living in Scotland is 67% higher than in the South West of England and 84% higher for women.Significant socio-economic differences in the mortality for CHD are evident. The premature deaths rate from CHD at the end of the 1980s for male manual workers was 58% higher than for male non-manual workers, while the premature death rate from CHD for female manual workers was more than twice as high.The highest deaths rates for CHD in the UK have been observed among South Asians (Indians, Bangladeshis, Pakistanis and Sri Lankans).

IV. ETIOLOGY

According to the World Health Organization, 11.6% of adults in the country have raised blood glucose, 28.8% have raised blood pressure, 10.4% are obese, and 43% of adult males are smokers. Much information has also been obtained from the National Health and Morbidity Survey (NHMS). The NHMS is carried out at 4 yearly intervals. It is a population-based, cross-sectional epidemiological study using two stage stratified method of sampling. It provides useful and valid data on the prevalence of risk factors for non-communicable diseases (NCD). In the NHMS adults aged 18 years and above were recruited. 32.7% were found to be hypertensive, two thirds of whom were newly diagnosed. The prevalence of diabetes was 15.2%, with more than half of them newly diagnosed. 35.1% had hypercholesterolemia (serum total cholesterol >5.2 mmol/L). The high prevalence of coronary artery disease risk factors hypertension, diabetes mellitus, dyslipidaemia, smoking and obesity are also consistently reported in the NCVD database registry which publishes annual reports. The NCVD-ACS17 annual reports consistently report more than 95% of patients having at least one established cardiovascular risk factor on admission for ACS.

Most of the studies were done in urban populations with specialist cardiology services. In a case-control study done by Suleiman and colleagues18 in Hospital Kuala Lumpur, out of 102 patients who were admitted to the male medical ward, 44 were diagnosed as CAD and 58 with other diagnosis. Smoking and hypercholesterolemia were significant predictors of CAD diagnosis in this study. In another study, Ahmad and colleagues19 enrolled 525 patients with unstable angina or NSTEMI in 17 tertiary hospitals between 2004-2005 and found 96.8% with at least one established risk factor. Total of the 525 patients, 66.1% of patients had hypertension, 38.9% diabetes mellitus and 40.4% dyslipidaemia.

Diabetes mellitus, hypertension and hyperlipidaemia was 45.7%, 78.8% and 89.1% respectively. Indians had the highest prospensity of having all the three risk factors while Chinese and Malays most frequently presented with the combination of hypertension and hyperlipidaemia. There are a few studies on risk factors prevalence in the rural population. Collected data on the prevalence of CAD risk factors in rural Pahang from 1997-1999. The study recruited 609 subjects and found that the prevalence of CAD risk factors was comparable to that in the urban population: dyslipidaemia (67.3%), hypertension (30.3%), smoking (24.4%), diabetes (6.4%), impaired fasting glucose (13.9%), overweight/obesity (44.7%) and increased waist-to hip ratio (48.5%). Similarly, the prevalence of hypertension and smoking in rural Selangor, and found high prevalence of risk factors: 28.6% hypertensive and 21.1% smokers. However, a study in rural Sarawak found lower prevalence of risk factors: 13.5% hypertension, 1.5% diabetes, 15.4% smokers and 22.6% hypercholesterolemia.

V. PATHOPHYSIOLOGY

Limitation of blood flow to the heart causes ischemia (cell starvation secondary to a lack of oxygen) of the heart's muscle cells. The heart's muscle cells may die from lack of oxygen and this is called a myocardial infarction (commonly referred to as a heart attack). It leads to damage, death, and eventual scarring of the heart muscle without regrowth of heart muscle cells. Chronic high-grade narrowing of the coronary arteries can induce transient ischemia which leads to the induction of a ventricular arrhythmia, which may terminate into a dangerous heart rhythm known as ventricular fibrillation, which often leads to death.
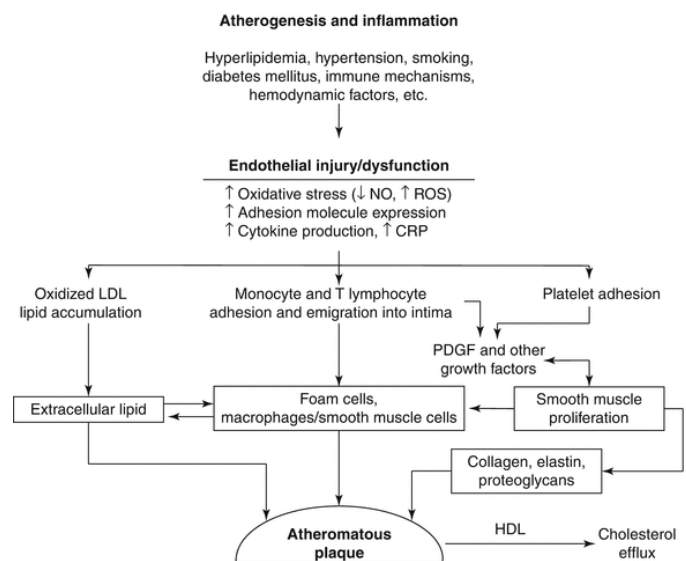

Figure 1: Pathophysiology of CAD

Typically, coronary artery disease occurs when part of the smooth, elastic lining inside a coronary artery (the arteries that supply blood to the heart muscle) develops atherosclerosis. With atherosclerosis, the artery's lining becomes hardened, stiffened, and accumulates deposits of calcium, fatty lipids, and abnormal inflammatory cells – to form a plaque. Calcium phosphate (hydroxyapatite) deposits in the muscular layer of the blood vessels appear to play a significant role in stiffening the arteries and inducing the early phase of coronary arteriosclerosis. This can be seen in a so-called metastatic mechanism of calciphylaxis as it occurs in chronic kidney disease and hemodialysis.

Although these people suffer from a kidney dysfunction, almost fifty percent of them die due to coronary artery disease. Plaques can be thought of as large "pimples" that protrude into the channel of an artery, causing a partial

obstruction to blood flow. People with coronary artery disease might have just one or two plaques, or might have dozens distributed throughout their coronary arteries. A more severe form is chronic total occlusion (CTO) when a coronary artery is completely obstructed for more than 3 months.

Cardiac syndrome X is chest pain (angina pectoris) and chest discomfort in people who do not show signs of blockages in the larger coronary arteries of their hearts when an angiogram (coronary angiogram) is being performed. The exact cause of cardiac syndrome X is unknown. One explanation is micro vascular dysfunction. For reasons that are not well understood, women are more likely than men to have it; however, hormones and other risk factors unique to women may play a role.
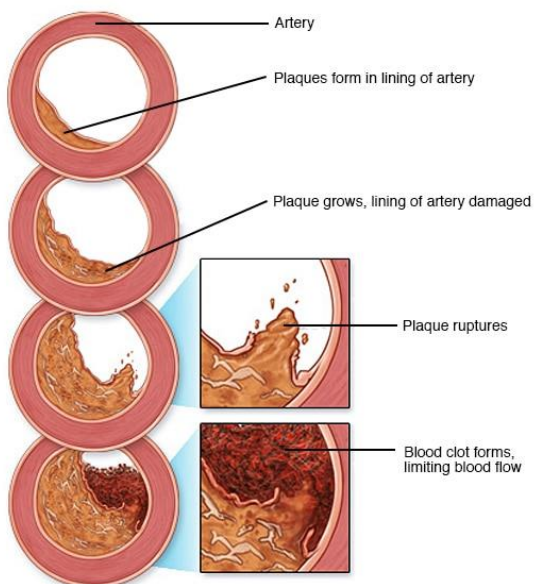
Figure 2: Plaque in Artery Wall

VI. SIGN AND SYMPTOMS

Common symptoms of coronary artery disease (CAD) include angina, shortness of breath (particularly during physical exertion), and rapid heartbeat. Sometimes patients with CAD have few or no symptoms until they have heart attack or heart failure.

A) Stable Angina and Chest Pain

Stable angina is predictable chest pain. Although less serious than unstable angina, it can be extremely painful or uncomfortable. It is usually relieved by rest and responds well to medical treatment (typically nitroglycerin). Any event that increases oxygen demand can cause an angina attack. Some typical triggers include:

- Exercise
- Cold weather
- Emotional tension
- Large meals

Angina attacks can happen at any time during the day, but most occur between 6 a.m. and noon.Other symptoms that may indicate angina or accompany the pain or pressure in the chest include:

- Shortness of breath
- Nausea, vomiting, and cold sweats
- A feeling of indigestion or heartburn
- Unexplained fatigue (more common in women)
- Dizziness or lightheadedness
- Palpitations

B) Unstable Angina and Acute Coronary Syndrome

Unstable angina is a much more serious situation and is often an intermediate stage between stable angina and a heart attack, in which an artery leading to the heart (a coronary artery) becomes completely blocked. A patient is usually diagnosed with unstable angina under one or more of the following conditions:

- Pain awakens a patient or occurs during rest.
- A patient who has never experienced angina has severe or moderate pain during mild exertion (walking two level blocks or climbing one flight of stairs).
- Stable angina has progressed in severity and frequency within a 2-month period, and medications are less effective in relieving its pain.
- Fainting episode.

C) Other Causes of Chest Pain or Discomfort

Chest pain is a very common symptom in the emergency room, but heart problems account for less than half of all chest pain episodes. There are many other causes of chest pain or discomfort including injured muscles, arthritis, heartburn, and asthma. Still, if you are experiencing chest pain, it is best to seek immediate medical attention.

VII. DIAGNOSIS

Many tests can diagnose possible heart disease. The choice of which (and how many) tests to perform depends on the patient's risk factors, history of heart problems, and current

symptoms. Usually the tests begin with the simplest and may progress to more complicated ones.

A) Routine Tests to Determine Risk for Heart Disease

Doctors routinely check for high blood pressure and unhealthy cholesterol levels in all older adults. Specific tests are also important in people who may have risk factors or symptoms of diabetes.

B) Electrocardiograms (ECGs)

An electrocardiogram (ECG) measures and records the electrical activity of the heart. Up to half of people who suffer from angina or silent ischemia, however, have normal ECG readings. The waves measured by the ECG correspond to when different parts of the heart contract and relax. The electrocardiogram (ECG, EKG) is used extensively in the diagnosis of heart disease, from congenital heart disease in infants to myocardial infarction and myocarditis in adults. Several different types of electrocardiogram exist.

- P Wave: The P wave is associated with the contractions of the atria (the two chambers in the heart that receive blood from outside).
- QRS: The QRS is a series of waves associated with ventricular contractions. (The ventricles are the two major pumping chambers in the heart.)
- T and U: These waves follow the ventricular contractions.
- The most important wave patterns in diagnosing and determining treatment for heart disease and heart attack are called ST elevations and Q waves.A depressed or horizontal ST wave suggests some blockage and the presence of a heart disease, even if there is no angina present. (This wave pattern is not very accurate, particularly in women, and can occur without heart problems).
- ST elevations and Q waves are the most important wave patterns in diagnosing and determining treatment for a heart attack. They suggest that an artery to the heart is blocked, and that the full thickness of the heart muscle is damaged. ST segment elevations, however, do not always mean the patient has a heart attack. Other factors are important in making a diagnosis.

C) Exercise Stress Test

Exercise stress test for evaluation of coronary artery disease may be performed in the following situations:

- Patients with possible or probable angina to help determine the likelihood of coronary artery disease being present
- Patients who were previously stable who began having symptoms
- Follow-up of patients with known heart disease or after coronary bypass surgery or percutaneous procedure
- To determine a patient's functional capacity (how well the heart can respond when extra demand is needed)
- Patients with certain types of heart rhythm disturbances
- After a heart attack, either before leaving the hospital or soon afterwards

Basic Procedure: A stress test (exercise tolerance test) monitors the patient's heart rhythms, blood pressure, and clinical status. It can tell how well the heart handles work and if parts of the heart have decreased blood supply.

- The patient walks on a treadmill or rides a stationary bicycle. Exercise continues until the heart is beating at least 85% of its maximum rate, until symptoms of heart trouble occur (changes in blood pressure, heart rhythm abnormalities, angina, and fatigue), or the patient simply wants to stop.
- For patients who cannot exercise, the doctor may administer dobutamine or arbutamine, which are drugs that simulate the stress of exercise.
- An ECG is used to monitor heart rhythms during a stress test. (An echocardiogram or more advanced imaging technique may also be used to visualize the actions of the heart and blood flow.)

Interpreting Results: To accurately assess heart problems, a variety of factors are measured or monitored using the ECG and other tools during exercise. They include:

- Exercise capacity: This is a measure of a person's capacity to reach certain metabolic rates.
- ST waves on the ECG: Doctors specifically look for abnormalities in part of the wave tracing called an ST segment. A certain type of ST segment depression may suggest the presence of heart disease. However, gender, drugs, and other medical conditions can affect the ST segment.
- Heart rate: This is how fast the heart rate goes during exercise and how quickly it returns to normal recovery. Based on age and other factors, everyone's heart rate should go up to a certain level during

exercise. If it does not go up to the expected level, the patient is considered at risk for heart problems.

- Changes in systolic blood pressure: Generally, the blood pressure will go up during exercise.
- Oxygen levels may also be measured.
- Using these and other measures, doctors can determine risk fairly accurately, particularly for men with chronic stable angina. The test has limitations, however, and some are significant. In patients with suspected unstable angina, normal or low risk results may not be as accurate in predicting future risk of cardiac events.
- About 10% of patients, particularly younger people, will have false positive test results. In such cases, test results indicate abnormalities when there are no heart problems. In addition, for many reasons, the test is less accurate in women and an echocardiogram may be a more accurate procedure for them.

D) Echocardiograms

An echocardiogram is a noninvasive test that uses ultrasound images of the heart. This test is more expensive than an ECG, but it can be very valuable, particularly in identifying whether there is damage to the heart muscle and the extent of heart muscle damage.

A stress echocardiogram may be performed to further evaluate abnormal findings from an exercise treadmill test or a routine echocardiogram. Examples include identifying exactly which part of the heart may be involved and quantifying how much muscle has been infected. It may be the first test done when the exercise treadmill test cannot be performed due to certain abnormal rhythms.

E) Radionuclide Imaging

Radionuclide procedures use imaging techniques and computer analyses to plot and detect the passage of radioactive tracers through the region of the heart. Such tracing elements are typically given intravenously. Radionuclide imaging is useful for diagnosing and determining:

- Severity of unstable angina when less expensive diagnostic approaches are unavailable or unreliable.
- Severity of chronic coronary artery disease.
- Success of surgeries for coronary artery disease.
- Whether a heart attack has occurred.

F) Myocardial Perfusion (Blood Flow) Imaging Test (also called the Thallium Stress Test): This radionuclide test is

typically used with an exercise stress test to determine blood flow to the heart muscles. It is a reliable measure of severe heart events. It may be useful in determining the need for angiography if CT scans have detected calcification in the arteries. About a minute before the patient is ready to stop exercising, the doctor administers a radioactive tracer into the intravenous line. (Tracers include thallium, technetium, or sestamibi.) Immediately afterwards, the patient lies down for a heart scan. If the scan detects damage, more images are taken 3 or 4 hours later. Damage due to a prior heart attack will persist when the heart scan is repeated. Injury caused by angina, however, will have resolved by that time.

G) Radionuclide Angiography: This is a technique for visualizing the chambers and major blood vessels of the heart. It uses an injected radioactive tracer and can be performed during exercise, at rest, or with use of stress-inducing drugs. It can help determine the severity of coronary artery disease and is an alternative to echocardiograms in certain situations

H) Angiography

Angiography is an invasive test. It is used for patients who show strong evidence for severe obstruction on stress and other tests, and for patients with acute coronary syndrome. It is required when there is a need to know the exact anatomy and disease present within the coronary arteries. A limitation of angiography is that it is not always the most occluded (narrowed) artery that causes the next heart attack. In an angiography procedure:

- A narrow tube is inserted into an artery, usually in the leg or arm, and then threaded up through the body to the coronary arteries.
- A dye is injected into the tube, and an x-ray records the flow of dye through the arteries.
- This process provides a map of the coronary circulation, revealing any blocked areas
- **Magnetic Resonance Angiography (MRA):** MRA is a newer noninvasive imaging technique that can provide three-dimensional images of the major arteries to the heart.

VIII. COMPLICATIONS

Coronary artery disease can lead to:

- **A) Chest pain (angina):**When your coronary arteries narrow, your heart may not receive enough blood when demand is greatest — particularly during physical activity. This can cause chest pain (angina) or shortness of breath.

B) **Heart attack:**If a cholesterol plaque ruptures and a blood clot forms, complete blockage of your heart artery may trigger a heart attack. The lack of blood flow to your heart may damage your heart muscle. The amount of damage depends in part on how quickly you receive treatment.

C) **Heart failure:** If some areas of your heart are chronically deprived of oxygen and nutrients because of reduced blood flow, or if your heart has been damaged by a heart attack, your heart may become too weak to pump enough blood to meet your body's needs. This condition is known as heart failure.

D) **Abnormal heart rhythm (arrhythmia):** Inadequate blood supply to the heart or damage to heart tissue can interfere with your heart's electrical impulses, causing abnormal heart rhythms.

IX. TREATMENT AND MANAGEMENT

A) DRUGS

Various drugs can be used to treat coronary artery disease, including:

1. **Cholesterol-modifying medications.** By decreasing the amount of cholesterol in the blood, especially low-density lipoprotein (LDL, or the "bad") cholesterol, these drugs decrease the primary material that deposits on the coronary arteries. Your doctor can choose from a range of medications, including statins, niacin, fibrates and bile acid sequestrants.

2. **Aspirin:**Your doctor may recommend taking a daily aspirin or other blood thinner. This can reduce the tendency of your blood to clot, which may help prevent obstruction of your coronary arteries.If you've had a heart attack, aspirin can help prevent future attacks. There are some cases where aspirin isn't appropriate, such as if you have a bleeding disorder or you're already taking another blood thinner, so ask your doctor before starting to take aspirin.

3. **Beta blockers:** These drugs slow your heart rate and decrease your blood pressure, which decreases your heart's demand for oxygen. If you've had a heart attack, beta blockers reduce the risk of future attacks.

4. **Nitroglycerin:** Nitroglycerin tablets, sprays and patches can control chest pain by temporarily dilating your coronary arteries and reducing your heart's demand for blood.

5. **Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs):**These similar drugs decrease blood pressure and may help prevent progression of coronary artery disease.

B) SURGERY

1. Angioplasty and Stents

Angioplasty, also called percutaneous coronary intervention (PCI), involves procedures such as percutaneous transluminal coronary angioplasty (PTCA) that help open the blocked artery.

Angioplasty can help reduce the frequency of angina attacks for patients who have not been helped by drug therapy. It is commonly recommended for patients who have critically blocked arteries or have already had a recent, acute heart attack. Angioplasty can also help improve survival and prevent heart attacks in patients with acute coronary syndrome (ACS). However, doctors have been uncertain about angioplasty's benefits for survival and heart attack prevention in lower-risk patients with stable coronary artery disease. Angioplasty works no better than standard heart medication (drugs to control blood pressure, lower cholesterol, and prevent blood clots) in preventing heart attack, stroke, and hospitalization in patients with stable coronary artery disease. Doctors now recommend angioplasty only for patients who have severe heart disease. For patients with stable heart disease, drug therapy may be sufficient enough treatment and allow them to safely defer having surgery.
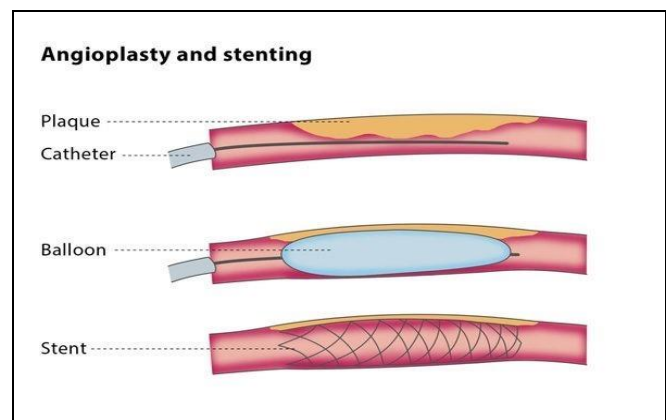

Figure 3: Angioplasty and Stenting

Procedure: A typical angioplasty procedure follows these steps:

- The cardiologist threads a narrow catheter (a tube) containing a catheter from the groin area into the blocked vessel.
- The doctor opens the blocked vessel using balloon angioplasty, in which the surgeon passes a tiny deflated balloon through the catheter to the vessel.

- The balloon is inflated to compress the plaque against the walls of the artery, flattening it out so that blood can once again flow through the blood vessel freely.
- To keep the artery open afterwards, doctors use a device called a coronary stent, an expandable metal mesh tube that is implanted during angioplasty at the site of the blockage. (In some cases, a stent may be used as the initial opening device instead of balloon angioplasty.) The stent may be bare metal or it may be coated with a drug that slowly releases medication.

Recuperation and Complications:

- Angioplasty is less invasive than bypass surgery, requiring only one night in the hospital. Recuperation takes about a week. Chest pain after the procedure is very common and usually due to problems other than ischemia. Mild chest pain is even more common when a stent is used, possibly because the artery is stretched.
- The most important short- and long-term complication of angioplasty is narrowing or reclosure (restenosis) of the artery, which can lead to heart attack if not treated with a repeat procedure. Stenting, anti-clotting drugs, and other advances have significantly helped prevent reclosure and reduce heart attack rates. Nevertheless, a repeat procedure is still needed to restore the opening in 10 - 15% of patients who have stents.

Drug-Coated Stents: Stents coated with the drugs sirolimus (Rapamune) or paclitaxel (Taxol) have been increasingly used in the last several years. Drug-eluting stents (as they are also called) can help prevent restenosis. However, because drug-eluting stents reduce arterial tissue growth, they can increase the risks of blood clots.
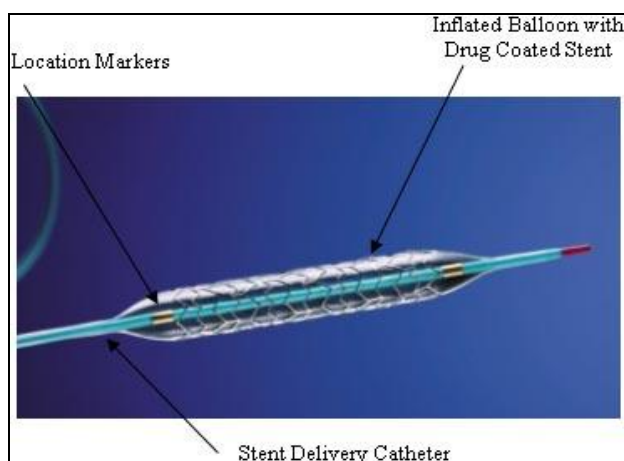

Figure 4: Drug Coated Stent

- Recent studies indicate that drug-eluting stents are safe and effective for patients with coronary artery disease when they are used for FDA-approved indications. Some studies have indicated that problems may arise when these stents are used for "off-label" purposes in patients with more complicated health problems, although other studies have found no increased risks. There is still some concern that all stents (both bare metal and drug eluting) may be used too frequently for patients who may be better served by drugs or bypass surgery.
- It is very important that all patients who have drug-eluting stents take aspirin and clopidogrel for at least 1 year after the stent is inserted to reduce the risk of blood clots. For patients undergoing PCI who have acute coronary syndrome, two newer antiplatelet drugs – prasugrel (Effient) or ticagrelor (Brilinta) – may be options. These drugs, like aspirin, help prevent blood platelets from clumping together. It is important that patients who have drug-eluting stents take both aspirin and another anti-platelet drug. If for some reason patients cannot stick to a dual anti-platelet regimen, they should receive a bare metal stent instead of a drug-eluting stent.

2. **Coronary Artery Bypass Graft Surgery**

- Coronary artery bypass graft surgery (CABG) is an alternative to angioplasty for many patients with severe coronary artery disease, but it is a very invasive open-heart surgical procedure.
- Minimally invasive coronary artery bypass surgery (MIDCAB), also called "keyhole heart surgery," may be an option for some patients. It uses various techniques, including endoscopy or robotic-assisted approaches. Unlike standard CABG, with MIDCAB patients do not have their heart stopped and do not have to be put on a heart-lung machine during the procedure. In MIDCAB, the surgeon uses a smaller incision on the left side of the chest. CABG requires a longer incision down the center of the chest.

In a traditional CABG procedure:

- The chest is opened, and the blood is rerouted through a lung-heart machine.
- The heart is stopped during the procedure.
- Blood vessel grafts are taken from arteries or veins in the chest wall or other areas of the body. The grafts are transplanted in front of and beyond the blocked arteries, so the blood flows through the new vessels around the blockage. Patients may require one, two,

or three grafts (or more) depending on the number of coronary arteries that are blocked.

- In general, patients with triple bypass procedures stay in the hospital for 5 or 6 days. Those with one-vessel bypass may be able to go home in 3 days.

Complications: Complications are generally rare but can include bleeding, infections, heart attack, and stroke. Finding a surgeon who performs at least 100 of the procedures a year helps reduce the risk for complications.

Blood clots may form in the new graft, closing it up or narrowing the treated vessel over time. Therapy with aspirin and other anti-clotting drugs help keep the graft open and working properly.

Recuperation and Rehabilitation: After leaving the hospital, patients should have cardiac rehabilitation. Guidelines recommend that doctors refer patients who have had CABG or PCI to a comprehensive outpatient cardiac rehabilitation program. Rehabilitation includes education about healthy diet and lifestyle choices, as well as exercise training to rebuild strength and stamina.

Treatment for coronary artery disease usually involves lifestyle changes and, if necessary, drugs and certain medical procedures.

3. Lifestyle changes:

Making a commitment to the following healthy lifestyle changes can go a long way toward promoting healthier arteries:

- Quit smoking.
- Eat healthy foods.
- Exercise regularly.
- Lose excess weight.
- Reduce stress.

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