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Percutaneous Coronary Intervention: Review Article

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Abstract:

Percutaneous coronary intervention (PCI) is the most common technique to improve myocardial perfusion when treating coronary artery disease. It is very efficacious in improving symptoms for individuals with stable angina, and improves prognosis in acute coronary syndromes, particularly in the emergency treatment of patients presenting with ST elevation myocardial infarction. It is performed via a small intra-arterial sheath. A balloon is used to dilate the coronary stenosis, and a stent is implanted to scaffold the vessel. Re-narrowing at the treated site can occur but has been greatly reduced by drug-eluting stents. Most acute complications of PCI are mediated by platelet activation, so drugs blocking platelet aggregation are pivotal to the procedure's safety. Early complications include haemorrhage from the arterial access site (reduced by a radial approach). Abrupt vessel closure, stroke, vessel perforation and tamponade are rare. The requirement for emergency cardiac surgery is <0.1%, and in-hospital mortality is mainly determined by the indication for PCI – about 0.2% in patients with stable angina, 5% after ST elevation myocardial infarction and 30–50% in the context of cardiogenic shock. Technical advances mean that patients with complex coronary artery disease and co-morbid conditions can now be treated by PCI.

Keywords: Percutaneous Coronary Intervention, CAD, MI.

Introduction:

Worldwide, coronary artery disease (CAD) is the leading cause of morbidity and mortality and imposes a major health and economic burden on the majority of developed nations. In the United States alone it is estimated to cause 790,000 heart attacks each year **(1).**

In the past decade, improved therapies have decreased the mortality accompanying CAD while increasing survival following a myocardial infarction. Despite this decrease in mortality, the prevalence of CAD is expected to continue to increase due to the increase in the aging population **(2).** The treatment of CAD has been transformed by the introduction of percutaneous coronary intervention (PCI), which remains the focus of intensive research and development **(3).**

The first milestone in treating CAD was achieved by the introduction of Balloon angioplasty performed by Andreas Grüntzig in 1977. However, this technique had two major drawbacks: Thrombosis and acute occlusion caused by vascular elastic recoil occurred in 5–10% of patients immediately after the procedure, and development of neointimal proliferation with restenosis occurred in ~30% of patients within the first six months. In an effort to combat the shortcomings of elastic recoil, pioneering work performed by Sigwart et al. developed and implanted the first self-expanding bare-metal stent (BMS) following balloon angioplasty, and in 1987 the BMS was the first food and drug administration (FDA)-approved stent in the USA **(4).**

Indications:

The following are the clinical indications that could require a percutaneous coronary intervention.

- Acute ST-elevation myocardial infarction (STEMI)
  - In the first 12 h after onset of symptoms.
  - Between 12 and 24h after symptoms onset, routine primary PCI is indicated.
  - In 2017 guidelines, routine primary PCI in asymptomatic patients presenting at 24–48h should be considered.
  - After 48h, routine opening of an occluded IRA is not recommended in 2017 guidelines. In cases of ongoing ischaemic symptoms or haemodynamic or electrical instability, a primary PCI strategy is always recommended regardless of time from onset of symptoms **(5)**
- Non–ST-elevation acute coronary syndrome (NSTE-ACS)
  - Early invasive therapy (within 2 hours of symptoms) recommended with refractory angina, recurrent angina, symptoms of heart failure, new or worsening mitral regurgitation, hemodynamic instability, or sustained ventricular tachycardia/fibrillation.
  - A worsening of troponin levels should trigger an early therapy (within 24 hours)
- Unstable angina and chronic coronary syndrome
- Anginal equivalent (e.g., dyspnea, arrhythmia, or dizziness or syncope)
- High-risk stress test findings
- PCI is indicated for critical coronary artery stenosis, which does not qualify for coronary artery bypass surgery (CABG) **(6)**

Equipment:

- Percutaneous coronary intervention is performed during an angiogram in the angiography suite. Other than standard equipment, the following supplies may be used on a case-to-case basis.
- Introducer needle, sheath introducer, guide catheters, radio-opaque dye (IV contrast), guidewire, balloon catheter, stents (bare metal stents or drug-eluting stents which are found to have reduced restenosis and revascularization rates compared with bare metal ones), drug-eluting balloons (DEB) and thrombus aspiration (not recommended routinely). Additional devices may be used, e.g: atherectomy devices (rotational atherectomy, laser, cutting balloons, radiation beads and lithoplasty/ lithotripsy systems) **(7)**

Technique:

Access: Coronary angiography and percutaneous coronary intervention (PCI) are more commonly performed via the femoral or the radial artery and less commonly performed via the brachial or ulnar artery. Overall, the femoral artery is the most common route of access for these procedures in the United States; however, the use of radial access is increasing. In selected labs in the United States and in some parts of Europe, radial artery access exceeds 90 % **(8).**

The European Society of Cardiology (ESC) guidelines on STEMI patients recommend preference of radial over femoral access, if it is performed by an experienced radial operator (class IIa, level B). The Society for Cardiovascular Angiography and Interventions released a consensus statement on best practices for the use of radial access for diagnosing and treating coronary artery disease (CAD), focusing on avoiding radial artery occlusion, reducing radiation exposure, and using the transradial approach in STEMI (**9).**

Procedure:

For transradial catheterization, an arteriotomy is made approximately 2 cm proximal to the radial styloid process so as to avoid the distal bifurcation and diminutive vessels. While palpation is being done, the radial artery is punctured with a micropuncture needle, and a hydrophilic sheath is placed by means of the modified Seldinger technique (**10).**

Once the sheath is in place, an intra-arterial vasodilator is given (nicardipine 500 μg or verapamil 5 mg), with half the dose administered at the beginning of the procedure and the other half at the end. Intravenous (IV) heparin dramatically reduces the risk of radial artery occlusion and is therefore often used in transradial catheterization (usual dose, 50 units/kg; maximum total dose, 5000 units) (**11**).

For transfemoral catheterization, the arteriotomy site is the common femoral artery, above its bifurcation into the deep femoral artery (profunda femoris) and the superficial femoral artery and below the inferior epigastric artery. Because the skin crease can sometimes be misleading, a combination of various other anatomic landmarks may be used, such as bony landmarks (aiming 2 cm below the center of the inguinal ligament) and the point of maximal palpable impulse (**12**).

Fluoroscopy is often used to mark the femoral head, and the target zone for the arteriotomy is the middle of the femoral head. A micropuncture (21-gauge) or 18-gauge needle is used to puncture the femoral artery, and a sheath is placed with the modified Seldinger technique. Sheath size varies according to the preference of the operator; in general, it is in the range of 4-6 French(**13**).

Once access is obtained, catheters are advanced over a 0.035-in. J-tip guide wire into the ascending aorta. Various different catheter shapes are available; the choice depends on the operator's preference and the patient's anatomy. Selective coronary angiography is performed in different views (at least two orthogonal views for each segment of the coronary) using hand or power injections of iohexol (**14**).

Guide catheters have the same external diameter as diagnostic catheters but a larger lumen and are used for PCI. Once the catheter has engaged the coronary ostium and diagnostic angiograms have been obtained, weight-based IV anticoagulant (unfractionated heparin (UFH), bivalirudin, or low-molecular-weight heparin (LMWH) therapy may be administered. If the patient is not on long-term dual antiplatelet therapy (DAPT), a loading dose of a P2Y12 inhibitor is also given. As noted above, all patients should have been pretreated with aspirin (**15**).

A 0.014-in. guide wire is then advanced into the coronary artery across the stenotic lesion. All balloon catheters and other devices will be tracked over this wire. In some cases, direct stenting of the lesion can be done; however, in most cases, vessel preparation with either predilation with a semicompliant balloon or an atherectomy device is performed. The balloon is then withdrawn, and a stent of appropriate length and diameter is advanced over the coronary guide wire, positioned across the lesion, and deployed (**16**).

Depending on the angiographic appearance of the stent, postdilation of the stent may or may not be performed with a noncompliant balloon. An intravascular imaging tool, such as intravascular ultrasonography (IVUS) or optical coherence tomography (OCT), can be used for further delineation and assessment of the anatomy including plaque burden, vessel size, and stent deployment. After the PCI result is deemed adequate, the coronary wire is removed and final angiograms are taken (**17**).

Post stenting dilatation outcome:

Percutaneous coronary intervention (PCI) has been widely used for patients with acute coronary syndrome (ACS), and the optimum coronary stent deployment is crucial to improve prognosis in the current practice of PCI. Stent underexpansion is usually the failure to achieve a minimal in-stent dimension of more than 80% of the average reference segment diameter in patients with PCI. Studies showed that late stent thrombosis and very late stent thrombosis are mainly related to malapposition (31%), while prominent mechanisms of acute stent thrombosis and subacute stent thrombosis are malapposition (48%) and underexpansion (26%) **(18).**

Underexpansion is a significant cause of restenosis **(19).** Thus, the postdilation of stent deployment is performed to achieve optimal stent expansion and complete the apposition of stent struts against the vessel wall **(20).** Studies indicated that the postdilation with a noncompliant balloon at higher pressure could reduce the restenosis rate and improve minimal stent area and minimal lumen diameter in unselected patients with stents implantation **(20).**

Prolonged inflation could increase stent expansion and strut apposition **(21)**, although overexpansion could increase neointimal hyperplasia caused by the inflammatory response to vessel wall injury and lead to an increased incidence of periprocedural myocardial infarction due to thrombus or plaque debris embolization in patients except for myocardial infarction and restenosis of the coronary artery **(22).**

However, vessel recanalization by primary percutaneous coronary intervention (PPCI) with drug eluting stents (DES) is the gold standard treatment for ST-segment elevation myocardial infarction (STEMI). Although stents are deployed over the commonly soft underlying lipid plaque and thrombus, optimal stent deployment in this setting is challenging due to factors like the presence and subsequent resolution of thrombus and vessel vasoconstriction **(23).** Stent optimisation with postdilatation using noncompliant (NC) balloons could improve deployment features as stent expansion and stent struts apposition **(24).**

Nevertheless, further device manipulation within the culprit vessel carries the risk of atherothrombotic material fragmentation and embolization to the distal vessel **(25).** Distal vessel embolization is a recognized cause of microvascular obstruction and therefore, postdilatation in the context of STEMI has been related with microvascular injury and the no-reflow phenomenon**(26).**

Studies regarding its benefits in STEMI patients undergoing PPCI have to date yielded inconsistent findings. Some studies have shown the improved immediate angiographic results and clinical outcomes following post-dilatation, whereas others have created the uncertainty about the utility and suggested the likely aggravation of microvascular obstruction and vessel wall injury**(27).**

Perfusion quantification after PCI:

Post infarction perfusion could be assessed by TIMI grade flow **(28),** corrected TIMI frame count (CTFC) **(29)** and TIMI myocardial perfusion (TMP) **(28).**

1. TIMI grade flow:

In 1983, the TIMI (Thrombolysis in Myocardial Infarction) study group (Brigham and Women's Hospital, Boston, Massachusetts) chose to conduct a randomized, double-blind, multicenter study to assess the efficacy of intravenous (IV) streptokinase. For this study, the TIMI Coronary Grade Flow was established to ensure a uniform and consistent method of recording epicardial perfusion on coronary arteriography. TIMI grade flow 0 represented total occlusion, and TIMI grade flow 3 represented normal epicardial perfusion. Images were evaluated at the clinical site and later at a central radiographic lab to further ensure consistency **(30)**

Grades of perfusion

- **Grade 0** (no perfusion): There is no antegrade flow beyond the point of occlusion.
- **Grade 1** (penetration without perfusion): The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine-angiographic filming sequence.
- **Grade 2** (partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. The rate of entry of the contrast material into the vessel distal to the obstruction or the rate of clearance from the distal bed is perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel—e.g., the opposite coronary artery or the coronary bed proximal to the obstruction.

- **Grade 3** (complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.**(28)**

Limitations of the TIMI grade flow include observer variability, and it only provides categorical values instead of continuous ones. However, the TIMI study group also developed additional scoring systems. TIMI frame count (TFC) measures the number of cine-angiographic frames to reach standardized distal landmarks, thus providing a quantitative assessment of epicardial flow. It was established to enhance the reproducibility of the angiographic assessment**(28).**

2. Corrected TIMI frame count (CTFC):

TIMI frame count is defined as the number of cineframes required for contrast to reach a standardized distal coronary landmark in the culprit vessel. The number is expressed based upon a cinefilming rate of 30 frames/second. Thus, a frame count of 30 would mean that 1 second was required for dye to traverse the artery **(31)**

The TIMI Frame Count is counted using an electronic frame counter. Selected anatomic landmarks are used for the analysis **(31)**

It was originally referred to as the "frames to opacification" but was later renamed the TIMI frame count **(32).**

A normal frame count is 21 ± 3 **(33).** TIMI grade 3 flow in coronary arteries after thrombolysis is actually slower than normal (35.6 ± 20.8). Furthermore, previous thrombolysis studies using TIMI flow assessments have assumed basal flow in the nonculprit artery to be normal. However, assessment of CTFC has demonstrated a 45% higher frame count (21 versus 31 frames) for basal flow in the uninvolved artery **(31).**

There are several limitations to the TFC classification scheme. To overcome these limitations, Gibson developed a more objective and precise index of coronary blood flow called the corrected TIMI frame count (CTFC). In this method, the number of cineframes required for dye to reach standardized distal landmarks are counted. Each frame is 1/30th of a second, and the angiogram is therefore essentially a measure of the time for dye to go down the artery **(33).**

In the first frame used for TIMI frame counting, a column of dye touches both borders of the coronary artery and moves forward. In the last frame, dye begins to enter (but does not necessarily fill) a standard distal landmark in the artery. These standard distal landmarks are as follows: in the RCA, the first branch of the posterolateral artery; in the circumflex system, the most distal branch of the obtuse marginal branch, which includes the culprit lesion in the dye path; and in the LAD, the distal bifurcation, which is also known as the "moustache," "pitchfork" or "whale's tail". These frame counts are corrected for the longer length of the LAD by dividing by 1.7 to arrive at the CTFC **(33).**

Knowing the time for dye to go down the artery from the CTFC (CTFC/30=seconds), and length of the artery (either from an angioplasty guide wire or by planimetry), dye velocity (cm/s) can also be calculated in a more refined fashion. This refined measure allows calculation of the velocity proximal and distal to the lesion **(34).**

In contrast to the TFG classification scheme, the CTFC is quantitative rather than qualitative, it is objective rather than subjective, it is a continuous rather than a categorical variable, and it is reproducible. The CTFC demonstrates that flow is not divided into arbitrary slow and fast categories, but rather coronary blood flow is unimodally distributed as a continuous variable **(33).**

The CTFC has been shown to be quite reproducible with a 1- to 2-frame difference between observers. The CTFC is also highly correlated with other measures of flow such as Doppler velocity wire measures of coronary flow reserve, distal velocity, average peak velocity, and volumetric flow **(35).**

3. TIMI myocardial perfusion (TMP):

As TIMI grade flow and TFC assess epicardial flow, TIMI myocardial perfusion (TMP) grade was developed to assess microvascular perfusion. Using myocardial contrast echocardiography, a visual assessment is made of

contrast density in the infarcted myocardium after reperfusion therapy. It is scored 0 to 3, with "0 representing no apparent tissue-level perfusion and TMP 3 indicating normal perfusion." It has been shown that despite having a TIMI grade flow of 3, some patients have no reflow in the myocardium (TMP 0). TMP has also been shown to be an independent predictor of mortality **(28).**

Grades of perfusion

- **Grade 0** (no perfusion): There is no antegrade flow beyond the point of occlusion.
- **Grade 1** (penetration without perfusion): The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine-angiographic filming sequence.
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- **Grade 3** (complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery **(36).**

Complications:

The common complications of PCI are bleeding, hematoma, and pseudoaneurysm at the access site. To minimize the risk of these complications, extreme care must be taken in obtaining access at the beginning of the procedure. Bleeding avoidance strategies (eg, bivalirudin and the radial approach) appear to lower the risk of post-PCI bleeding for both men and women; however, such strategies may be of particular significance in female patients, in that the absolute differences in risk are substantially greater in women (**37**).

A retrospective cohort analysis of data on 2,820,874 PCI procedures from the CathPCI registry demonstrated that the use of radial access for PCI (r-PCI) was on the increase and that the procedure was associated with a lower risk of bleeding and vascular complications than traditional transfemoral PCI, even after age, sex, and clinical presentation were accounted for (**38**).

Anaphylaxis caused by the contrast agent can occur; therefore, a careful preprocedural history must be obtained. Patients with a prior anaphylactoid reaction to the contrast media should receive appropriate steroid prophylaxis before repeat contrast administration. Contrast administration is one of the leading causes of hospital-acquired acute kidney injury (AKI). The only strategies that have been shown to minimize the risk of AKI are hydration and minimizing the use of contrast (**39**).

Contrast-induced nephropathy is defined as a rise in serum creatinine of at least 0.5 mg/dL or a 25% increase from baseline within 48 to 72 hours after contrast exposure. The Kidney Disease Improving Global Outcome (KDIGO) definition is different, with stage 1 being a rapid rise of creatinine to greater than 0.3 mg/dL within 48 hours or the relative rise of 50% or more from baseline in 7 days or less or a reduction in urine output to less than 0.5 ml/kg/hr for 6 to 12 hours. This severity is further staged based on creatinine levels, urine output, or the need for renal replacement therapy **(40).**

The mechanism by which balloon angioplasty or stenting improves luminal diameter is associated with significant local trauma to the vessel wall, which can, in turn, lead to occlusive complications in a minority of patients. Coronary artery dissection typically results from the vessel injury secondary to balloon expansion. Animal and postmortem human studies have shown that localized dissection at the site of balloon expansion is detected angiographically in as many as 50% of patients immediately after balloon angioplasty. Such small dissections probably are necessary to obtain adequate lumen expansion; they rarely interfere with antegrade blood flow and are usually

unimportant. Angiographic follow-up typically shows no residual evidence of a dissection as early as 6 weeks after angioplasty in most of the cases studied. However, larger dissections can lead to complications (**41**).

Often, these dissections are treated with a stent to cover the dissection flap. Coronary perforation or rupture is very rare (occurring in fewer than 1% of cases) and is typically associated with the use of ablative devices or oversized balloons. It can occur from the wire tip or at the culprit lesion. Wire perforations are typically small and usually do not warrant further intervention; perforations from balloon inflation or stent implantation can occasionally necessitate treatment with a covered stent graft. Abrupt vessel closure may occur in as many as 5% of balloon angioplasty cases, usually developing when the true lumen is compressed by a large dissection flap, thrombus formation, superimposed coronary vasospasm, or a combination of these processes. The presence of large coronary dissections immediately after balloon angioplasty is associated with a fivefold increase in the risk of abrupt closure (**41**).

Since the introduction and implementation of intracoronary stents and newer antiplatelet drugs, the incidence of abrupt closure has decreased significantly, to less than 1%. Microembolization of plaque debris or adherent thrombus may also cause acute complications during angioplasty and may contribute to postprocedural cardiac enzyme elevation and chest pain in some patients. In less than 1% of angioplasty patients, microembolization of the platelet-rich thrombus may cause diffuse distal arteriolar vasospasm secondary to release of vasoactive agents, resulting in no-reflow. This complication is difficult to treat but may respond to intracoronary calcium channel antagonists, adenosine, or nitroprusside. Patients undergoing balloon angioplasty of saphenous vein graft lesions and primary angioplasty in the setting of acute MI with a large amount of adherent thrombus are at greatest risk for distal embolization (**42**).

Some of the very rare but serious complications of PCI are stroke, MI, and death. With advances in technique, technology, and adjuvant medical therapy, PCI is now associated with mortality and emergency bypass rates lower than 1%. The rate of nonfatal MI after coronary angioplasty ranges from 5% to 15%, whereas the rate after stent placement ranges from 2% to 5% (**43**).

- **In-Stent Restenosis**

After balloon angioplasty or stent implantation, the vessel wall undergoes a number of changes. Platelets and fibrin adhere to the site within minutes of vessel injury. Within hours to days, inflammatory cells infiltrate the site, and vascular smooth muscle cells begin to migrate toward the lumen. The vascular smooth muscle cells then undergo hypertrophy and excrete an extensive extracellular matrix. During this period of vascular smooth muscle cell proliferation, endothelial cells colonize the surface of the lumen and regain their normal function **(44).**

Over the course of several weeks to months, multiple forces interact to cause remodeling of the vessel wall with either a decrease in lumen diameter (negative remodeling) or an increase in lumen diameter (positive remodeling). The amount of late loss in lumen diameter is dependent on the amount of neointimal proliferation and the degree of remodeling after intervention (see the image below). After 6 months, the repair process stabilizes and the risk of restenosis decreases significantly (**44**).

- **Stent Thrombosis**

Although DESs have significantly reduced the incidence of restenosis, early generations of these devices were linked with concerns regarding stent thrombosis. Currently, the thrombosis rate for a DES is virtually identical to that for a BMS at 1 year (0.5-0.7%). The NORSTENT study reported that the rates of definite stent thrombosis were 0.8% with DESs and 1.2% with BMSs (P = 0.05) over 6 years of follow-up. Late stent thrombosis (>1 year), which occurred with early-generation DESs, is rarely seen with current DESs (**45**).

The factor that makes the greatest contribution to stent thrombosis is interruption of antiplatelet therapy. Current guidelines recommend a minimum of 1 year of DAPT for DES patients with acute coronary syndrome, 6 months of DAPT for stable DES patients, and 1 month of DAPT for BMS patients. DESs take longer to endothelialize on the coronary vessel wall than BMSs do, and discontinuing DAPT may expose patients to an increased risk for stent thrombosis over time **(46).**

In some clinical situations (eg, before urgent noncardiac surgery in which antiplatelet therapy may have to be discontinued and when known or potential medicine compliance issues are present), implanting a bare-metal stent during PCI may be preferred to implanting a DES. Another important factor is final stent diameter and area. Underdeployment or incomplete apposition of any stent increases the risk of stent thrombosis. It was found that although stent thrombosis is infrequent, it results in higher rates of MI and death (**47).**

Evolution of drug-eluting stents:

- **History:**

Coronary stents were developed to overcome these shortcomings **(48).** The vast majority of PCI procedures performed currently involve angioplasty with stent deployment. Wallstent™, (Schneider AG, Bulach, Switzerland), a 'self-expanding, elastic, macroporous tubular prosthesis, woven from stainless steel', was the first stent implanted in a human coronary artery in 1984 **(4).**

In 1987, Schatz and co-workers developed the first stent to obtain US Food and Drug Administration approval (Palmaz-Schatz®; Johnson & Johnson, New Brunswick, NJ, USA). This was the first balloon-expandable, stainless-steel, tubular stent, and was widely used throughout the 1990s. In the early years of that decade, a number of other stents became available, including FlexStent® (Cook, Bloomington, IN, USA), Wiktor® (Medtronic, Minneapolis, MN, USA), Micro® (Applied Vascular Engineering, Twickenham, UK), Cordis® (Cordis, Santa Clara, CA, USA) and MULTI-LINK® (Advanced Cardiovascular Systems, Santa Clara, CA, USA) **(48).**

These bare metal stents (BMSs) reduced acute vessel closure and early elastic recoil; however, they were bulky, difficult to use and associated with frequent device failure. Furthermore, the risk of in-stent restenosis was significant due to proliferation and migration of vascular smooth muscle cells within the device **(49).** The use of stents, therefore, remained limited to cases of acute/threatened closure or restenosis after balloon angioplasty until two landmark trials, the Belgium Netherlands Stent Arterial Revascularization Therapies Study (BENESTENT) and the North American Stent Restenosis Study (STRESS), showed superiority of BMSs over balloon angioplasty **(50).**

- **Development of drug-eluting stents:**

Coating stents with anti-proliferative drugs, e.g., sirolimus or paclitaxel, substantially reduced in-stent restenosis. When incorporated within a polymer and coated on the surface of BMSs, these were released slowly over a few weeks after deployment. Eduardo Sousa implanted the first sirolimus-eluting stent in 1999 and it became available for clinical use as the CYPHER™ (Cordis) stent in 2002. CYPHER was tested in numerous randomised controlled trials (RCTs), demonstrating a significant reduction in in-stent restenosis and target vessel revascularisation (TVR) compared with BMSs **(51).**

TAXUS® (Boston Scientific), a paclitaxel-eluting stent, closely followed CYPHER, and again many RCTs (TAXUS I–IV) confirmed its efficacy against BMSs **(52).** Early-generation DESs, however, were linked with risk of stent thrombosis, possibly due to delayed endothelialisation by the anti-restenotic drugs or delayed hypersensitivity reaction to the polymer in DESs **(53).**

- **Components of a drug-eluting stent:**

There are three major components of a DES: the metallic platform, polymer (if present) and anti-proliferative drug **(54)**

Metallic platform; First-generation stents were typically made of stainless steel as it provides adequate radial strength to restore the patency of a stenotic artery. Although stainless steel remains a material used in some current-generation DESs (e.g., BioFreedom™, BioMatrix™ [Biosensors International, Singapore], Nobori® [Terumo, Tokyo, Japan]), alloys are more commonly employed. These include cobalt–chromium (e.g., XIENCE and Ultimaster™ [Terumo]), platinum–chromium (e.g., Promus and SYNERGY™ [Boston Scientific]) and nickel–titanium (also known as nitinol e.g., Xposition S [Stentys, Paris, France]). Some stents include two alloys, for example the Resolute

Onyx™ (Medtronic) stent has an outer shell of a cobalt-based alloy, but a platinum-iridium core in order to increase radiopacity **(55).**

Physical properties of commonly-used materials for metallic DES platforms are summarised in table 1. Compared to stainless steel, these alloys have intrinsically greater tensile strength whilst possessing similar or reduced elasticity. This allows manufacturing of thinner struts (typically >100 μm for stainless steel versus <100 μm for alloys) whilst maintaining strength, improving flexibility and deliverability, and reducing risk of stent thrombosis. Strut thickness and stent flexibility have an impact on the degree of injury, risk of rupture of the elastic laminae and overall inflammation, which may increase the risk of stent thrombosis events post-implantation. In addition, first-generation DES studies showed that thicker struts were associated with a higher incidence of side branch occlusion compared with thinner-strut DESs **(56)**. Moreover, thinner-strut devices have been associated with better clinical outcomes **(57)**

Table (1) : Physical properties of materials used for coronary metallic stent platforms **(54)**

Degradation time (months)	Elongation at break (%)	Tensile Elasticity (GPa)	Tensile Strength (MPa)	Material
Biostable	>40	193	668	**316L stainless steel**
Biostable	10–20	45	700	**Nitinol (nickel–titanium)**
Biostable	40	243	1,000	**L605 cobalt chromium**
Biostable	65	233	930	**MP35N cobalt chromium**
Biostable	45	203	834	**Platinum chromium**

Polymers; In first-generation DESs, the drug was incorporated in permanent (i.e., non-biodegradable) synthetic polymers such as polyethylene-co-vinyl acetate, poly-n-butyl methacrylate, and the tri-block copolymer poly (styrene-b-isobutylene-b-styrene).

Histopathological data indicated that the delayed vascular healing due to these polymer coatings may be associated with an increased risk of very late stent thrombosis after first-generation DES implantation.6 These polymers were superseded by more biocompatible permanent polymers (PPs) such as phosphorylcholine and a co-polymer of poly-vinylidene fluoride and hexafluoropropylene. Further development of DESs has led to those with biodegradable polymers, the rationale for these being that they behave as a conventional DES in the early phase and, once all the drug has been released and the polymer degraded, revert to a BMS as only the metallic platform remains. These typically utilise polylactic acid or a variation thereof as the polymer, which is broken down by hydrolysis over a period of months to lactic acid **(54)**

Anti-proliferative drugs; Amongst a variety of immunosuppressive and anti-proliferative agents tested to-date, mammalian target of rapamycin inhibitors have prevailed. Contemporary stents are mostly sirolimus-eluting stents, everolimus-eluting stents, zotarolimus-eluting stents or biolimus-eluting stents. Characteristics of these four commonly-used anti-proliferative drugs are shown in table 2. However, the search for a better drug continues, and other drugs, including novolimus and myolimus, are being tested **(58).**

Table (2) : Chemical and pharmacological properties of anti-proliferative agents commonly-utilized in drug-eluting stents **(54).**

Stent examples	MW (Da)	Drug
Promus SYNERGY XIENCE	954	**Everolimus**
Orsiro Ultimaster Xposition S	914	**Sirolimus**
BioMatrix Nobori BioFreedom	986	**Umirolimus (Biolimus A9)**
Resolute	966	**Zotarolimus**

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