Comparison of restenosis rates of two coronary stent systems with different active coating
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Dedicated to

My father
Haitham

My mother
Hana

My wife
Baraha

My sister and brothers
Barea, Nabil, Tamim

My children
Hana, Haitham
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5. Summary
1- Introduction:

1.1. Background:
Since the first human percutaneous transluminal angioplasty (PTCA) was performed in 1977, the use of this procedure has increased dramatically, becoming one of the most common medical interventions performed. The technique, initially developed in Switzerland by Andreas Grüntzig, has transformed the practice of revascularization for coronary artery disease (CAD) [20]. The growth of percutaneous coronary interventions (PCI) has been remarkable, more than one million PCIs are performed worldwide each year. Subsequently, the concept of endovascular prostheses (Stents) was developed. In 1987 Sigwart et al. reported the successful implantation of stents into coronary arteries of 8 patients [53]. In 1994 two large trials demonstrated the superiority of stenting over conventional angioplasty with reductions of restenosis rates by 30% compared to balloon angioplasty [15, 50]. Advances in catheter technology, operators experience, and adjunctive drug therapy have improved early outcomes after PTCA, procedural success > 90% and complication rates < 5% are readily achieved. Despite these advances, long-term outcome is still limited by restenosis. Depending on the definition used, angiographic restenosis has been reported in as many as 50% of patients within 6 months after balloon angioplasty which required repeated revascularization in approximately 20-30% of patients. Although stent implantation has been shown to reduce restenosis as compared with PTCA, in-stent restenosis (ISR) still occurs in 10-30% of the patients [64].

Following successful PTCA and stent implantation, intimal repair processes are initiated leading to restenosis in the treated vessel segment.

Experimental evidence suggests five major mechanisms causing restenosis after PTCA and stent implantation: 1- elastic recoil, 2- thrombus formation,
3- inflammation, 4- proliferation of vascular smooth muscle cells (VSMCs), and 5- excessive production of extra-cellular matrix. As elastic recoil is counteracted by stent, this mechanism is currently of minor importance [22, 26, 64].

Vessel injury by PTCA or stent strut leads to the activation of platelets and mural thrombus formation. The presence of vascular injury, mural thrombus, and metallic foreign body activates circulating neutrophils and tissue macrophages. These cells release cytokines and growth factors that activate smooth muscle cells (VSMCs). Up-regulation and expression of genes such as c-myc that regulate cell division, leading to cell proliferation. Production of matrix metalloproteinase is also up-regulated, leading to remodeling of the extra-cellular matrix, and initiating smooth muscle cell migration. The end result of this cascade of events is the uncontrolled proliferation of VSMCs around the vessel intima and the deposition of extra-cellular matrix material, which often lead to significant luminal narrowing 3 to 6 months after PCI [1]. Until recently, the only effective treatment for ISR was brachytherapy which reduces target vessel revascularization (TVR) rates and binary restenosis rates.

Although effective, brachytherapy has remained a technology with limited availability due to difficult logistic and radioactive materials. In contrast, drug-eluting stents containing the immunosuppressive agent (Rapamycin) and the anti-mitotic agent (Paclitaxel) have shown encouraging reductions in restenosis in de novo lesions, and possibly in ISR lesions [30].

1.2. Definitions of Restenosis:

When considering restenosis, three different aspects can be detected. First, **histological restenosis** refers to the process that occurs at the cellular level within the vessel. The second aspect is **angiographic restenosis**, which can be measured either by visual inspection of the angiography or by quantitative coronary
angiography (QCA). Finally, **clinical restenosis** refers to the occurrence of clinical events related to restenosis leading to symptoms or ischemia and accordingly to symptom-or ischemia-driven repeat revascularization of the vessel that was initially treated [60].

1.2.1. Angiographic Restenosis:

Over the last two decades, many definitions for angiographic restenosis have been used. Several of those are listed in (Table-1). The common definition is diameter stenosis (DS%) > 50% at follow-up, which was based on early studies showing impaired coronary flow reserve in such lesions [60].

Table-1. Angiographic Definitions of Restenosis

| 1- EMORY: | Diameter stenosis > 50% at follow-up. |
| 2- NHLBI I: | Increase in diameter stenosis > 30% at follow-up (compared to immediately after intervention). |
| 3- NHLBI II: | Residual diameter stenosis < 50% after PTCA increasing to >70% at follow-up. |
| 4- NHLBI III: | Increase in diameter stenosis at follow-up to within 10% of the diameter stenosis before PTCA. |
| 5- NHLBI IV: | > 50% loss of the initial gain achieved after PTCA. |
| 6- THORAXCENTER IIA: | > 0.72 mm loss in lumen diameter at follow-up. |

Abbreviations: NHLBI = National Heart, Lung, and Blood Institute. 

Depending on which definition is chosen, restenosis rates can vary widely (Figure-1).

As shown in Figure-1, no two definitions can completely encompass the restenotic process as measured by angiography.

Studies by Serruys and Nobuyoshi performed in the late 1980s unequivocally confirmed that angiographic restenosis tends to develop between 2 and 6 months after coronary angioplasty [35, 52].
<table>
<thead>
<tr>
<th>Pre-PTCA</th>
<th>Post-PTCA</th>
<th>Follow-up</th>
<th>Medical</th>
<th>Angiographic</th>
<th>Restenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>300% increase in MLD</td>
<td>1.6 mm</td>
<td>0.8 mm</td>
<td>Success</td>
<td>Failure</td>
<td>Yes</td>
</tr>
<tr>
<td>0.4 mm</td>
<td>50% decrease in MLD</td>
<td></td>
<td>Failure</td>
<td>Failure</td>
<td>Yes</td>
</tr>
<tr>
<td>3.2 mm</td>
<td>1.6 mm</td>
<td>0.4 mm</td>
<td>Success</td>
<td>Success</td>
<td>No</td>
</tr>
<tr>
<td>2.8 mm</td>
<td>42% decrease in MLD</td>
<td></td>
<td>Success</td>
<td>Success</td>
<td>No</td>
</tr>
<tr>
<td>600% increase in MLD</td>
<td>2.8 mm</td>
<td>2.8 mm</td>
<td>Success</td>
<td>Success</td>
<td>No</td>
</tr>
</tbody>
</table>

Figure -1. Example of variations in outcome according to the definition of restenosis. The reference diameter remains constant at 3.2 mm for all examples. In example 1, an intermediate improvement in the MLD of 300% results in a lumen 1.6 mm (50% diameter stenosis). An encroachment of 0.8 mm results in a 50% decrease in MLD and a significant 75% residual stenosis. In example 2, further encroachment leads to a 75% decrease in MLD (88% diameter stenosis) and recurrent angina. Restenosis occurs in both cases if either definition A (Def. A > 50% diameter stenosis at follow-up) or definition B (Def. B > 0.72 mm decrease in MLD from postoperative to follow-up) is used. In example 3, a 600% improvement in MLD and the same amount of encroachment during follow-up as in example 1 results in an MLD at follow-up of 1.6 mm (50% diameter stenosis). Restenosis occurs according to Def. B, because a decrease of 0.8 mm in MLD is present, but not if Def. A is used in example 4, the initially excellent results are maintained with the absence of restenosis either definition.

1.2.2. Comparative Measurements:
Important insights into understanding mechanisms of restenosis come from the relationship between lumen diameter at baseline, immediately after intervention, and during follow-up, expressed as acute gain and late loss (Figure-2).

**Acute gain**, defined as the difference in lumen diameter before and immediately after intervention, is due to plaque removal and/or arterial expansion. **Late loss**, defined as the difference in lumen diameter after intervention and at follow-up, reflects the net effects of intimal hyperplasia, elastic recoil, and vascular remodeling. Several studies have shown that the relationship between acute gain and late loss is constant irrespective of the device. For every 1 mm acute gain in lumen diameter, 0.5 mm is lost over 3-6 months (i.e., 50% of the initial gain is lost). **Loss index** is the ratio of late loss to acute gain a typical loss index is 0.5 [60].

1.3. Mechanisms of In-Stent Restenosis (ISR):
Over-distention of the diseased vessel causes endothelial disruption, internal elastic lamina fracture, and medial dissection. Lumen enlargement is caused by a combination of plaque reduction (compression/ embolisation), axial plaque redistribution towards the proximal and distal segments outside the stent, plaque extrusion, and vessel expansion. Many processes then contribute to restenosis [30].

1.3.1. Arterial Remodeling:
Negative remodeling is a major cause of human angioplasty restenosis, where > 40% of specimens retrieved at necropsy shown no evidence of neointima formation. Intravascular ultrasound studies also show that remodeling causes between two thirds and three quarters of the lumen loss in restenosis lesions. Although remodeling is largely negated by stenting, the mechanisms that contribute to remodeling are
unknown, or whether remodeling represents primarily a medial or adventitial response to injury [30].

![Graph showing continuous indices (acute gain, late loss, net gain, and loss index) related to the minimum lumen diameter (MLD) of the coronary vessel. These indices allow the sensitive, objective evaluation of serial changes in vascular dimensions after PTCA.](image)

Figure-2. Continuous indices (acute gain, late loss, net gain, and loss index) related to the minimum lumen diameter (MLD) of the coronary vessel. These indices allow the sensitive, objective evaluation of serial changes in vascular dimensions after PTCA. [From Kuntz RE, Safan RD, Levine MJ, et al. (1992): Novel approach to the analysis of restenosis after the use of three new coronary devices. J Am Coll Cardiol 19, 1493-1499].

**1.3.2. Thrombus Formation:**

Angiography or stenting causes endothelial denudation and induces medial dissection. The consequent exposure of sub-intimal components such as collagen, von Willebrand factor, fibronectin, and laminin causes platelet adhesion and aggregation. Fibrin and platelet are deposited on stent struts early after implantation. The association of fibrin and platelets with neointimal accumulation and extensive neovascularization at ISR sites suggests that organization of mural thrombus promotes ISR [30].
1.3.3. Neointimal Proliferation:

Arterial injury induces vascular smooth muscle cell (VSMC) proliferation and migration due to: 1- mechanical stretch, IEL rupture, and medial dissection, 2- endothelial denudation with exposure to circulating mitogens such as angiotensin II and plasmin, and 3- release of mitogens and cytokines from platelets, endothelial cells, VSMCs, and inflammatory cells. VSMCs are normally in the quiescent (G0) phase of the cell cycle. In animal models, injury induces medial and then intimal cell cycle entry, following a wave of immediate early gene expression. Cells undergo either cell proliferation or migration or both, with subsequent synthesis of extracellular matrix and collagen, resulting in neointima formation [30]. Neointima formation is the major cause of ISR.

Neointima increases up to three months after procedure, with little change to six months, and a gradual reduction between six months and three years. However, the role of cell proliferation within the neointima remains controversial. Cell proliferation is low in specimens retrieved from ISR sites, although higher ISR versus angioplasty restenosis sites. Although neointima formation after stenting is associated with medial disruption (extent of injury), proliferation does not correlate with time of injury. In contrast, most proliferating cells are located deep, adjacent to stent struts, suggesting that proliferation is a chronic low-grade reaction to the stent [14, 64].

Importantly, the restenotic lesion after angioplasty or stenting is hypocellular compared with primary plaques, consisting of collagen and matrix proteoglycans produced by limited VSMCs. Indeed, cells comprise only 11% of the tissue mass in human post-angioplasty neointima. ISR also consists of matrix proteoglycans and collagen, with decreasing cellularity and increasing matrix as ISR develops. This lack of VSMC proliferation in ISR clearly may reduce the expected benefit of treatment.
aimed solely at cell proliferation, compared with those that additionally alter matrix synthesis. Neointima formation within a stent also results from mechanisms, such as axial movement of primary plaque displaced to adjacent artery segment by the original procedure. Although this may represent VSMC migration, true VSMC migration from the media or adventitia adjacent to the angioplasty site analogous to that seen in animal models has not been conclusively demonstrated in humans [30]. Vascular smooth muscle cells exhibit several growth responses to agonist that regulate their function including proliferation (hyperplasia with an increase in cell number), Hypertrophy (an increase in cell size without change in DNA content), end-reduplication (an increase in DNA content and usually size), and apoptosis. Both autocrine growth mechanisms (in which the individual cell synthesizes and/or secretes a substance that stimulates the same cell type to undergo a growth response) and paracrine growth mechanisms (in which the individual cells responding to the growth factor synthesize and/or secrete a substance that stimulates neighboring cells of another cell type) are important in VSMC growth. In many situations, autocrine and paracrine growth mechanisms occur simultaneously [7].

1.3.4. Inflammation:

Porcine and non-primate models of injury show a robust inflammatory reaction to injury, with early mononuclear cell infiltration from the lumen into the thrombus. Monocytes secrete fibrinolytic enzymes, which may remodel or resorb the thrombus. Human stented arteries also show acute inflammation early after implantation, especially when stenting is associated with medial injury or lipid core penetration, and restenosis is associated with core penetration and inflammation. Indeed, some inflammatory cells (predominantly macrophages) are found at all stages of stent stenosis. As described above, resolution of inflammation may therefore play an
important part in restenosis, in particular via fibrosis and resultant scar contraction of both the adventitia and media [30].

1.4. Angiographic Patterns of In-Stent Restenosis:

One classification during the Palmaz-Schatz stent era considered stent restenosis as focal (lesion length < 10 mm) or diffuse. Focal lesions accounted for 42% of stent restenosis and generally had favorable outcomes after repeat intervention, including late target lesion revascularization (TLR) in 19%. Focal lesion were further classified as articulation or gap lesions (reflecting widespread use of the Palmaz-Schatz stent), margin lesion at the stent edge, focal lesions in the body of the stent, or short, multifocal lesions (Figure-3). Diffuse lesions were classified as in-stent lesion in 22% (repeat TLR 35%), diffuse proliferative lesions extending beyond the stent margins in 30% (repeat TLR 50%), or total occlusion in 6% (repeat TLR 83%) [32].

1.5. Predictors of Restenosis:

Predictive factors for restenosis can be divided into three general categories.

Patient-related factors are characteristic of the patient, thereby generally affecting the risk of restenosis in all lesions. Lesion-related factors are characteristic unique to each lesion, which should affect the risk of restenosis independently, even for multiple lesions within the same patient. Procedure-related factors comprise methods used in the procedure itself, such as the therapies used during the procedure and the method used to reduce the stenosis (Table-2).

Most notorious are aorto-ostial lesions, chronic total occlusion, and diabetes. Recently, baseline positive remodeling – enlargement of the external elastic membrane at the target lesion by IVUS – was identified as an independent predictor of clinical restenosis after PTCA and atherectomy [45].
The strongest predictors of stent restenosis are the \textit{pattern of restenosis, lesion length, diabetes, total plaque burden, and final lumen cross-sectional area} after stenting by IVUS. The number and length of stents reflect total plaque burden, and are important predictors of stent restenosis. However, the presence of overlapping stents is not a predictor of restenosis (Table-3 [45]).
Table-2. Risk factors for restenosis.

<table>
<thead>
<tr>
<th>Patient Factors:</th>
<th>Yes</th>
<th>Maybe</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Variant angina</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Recent onset angina &lt; 2-6 m</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Unstable angina</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- IDDM</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Chronic dialysis</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Smoking</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>- Primary PTCA in acute MI</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hypercholesterolemia</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male gender</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Previous MI</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- Hypertension</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- Age</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- Previous restenosis</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesional Factors:</th>
<th>Yes</th>
<th>Maybe</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Long lesion &gt; 20 mm</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Multivessel / Multilesional</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- SVG (proximal and body)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Chronic total occlusion</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Collaterals to dilated vessel</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ostial stenosis</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Angulation &gt; 45</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- LAD stenosis</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- Eccentricity</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- Calcification</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- Bifurcation lesion</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- Thrombus</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- Proximal location</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- LIMA</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- SVG (distal anastomosis)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
### Procedural Factors:

- Positive remodeling
- Pressure gradient > 20 mmHg
- Residual stenosis > 30%
- No dissection present
- Balloon inflation variable
  - Number of inflation
  - Inflation time
  - Maximum inflation pressure
  - Balloon Material
  - Inflation technique

### Table 3. Predictors of stent restenosis.

- Major:
  - Pattern of restenosis.
  - Lesion length.
  - Diabetes mellitus.

- Minor:
  - Final post-procedure lumen dimensions.
  - Total plaque burden.

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### 1.6. Prevention of Restenosis:

#### 1.6.1. Prevention of restenosis after PTCA:

**A-Pharmacological Interventions** [45]: Over the last decade, there have been numerous clinical trials of fish oil, corticosteroids, cytostatic agents, calcium channel blockers, lipid lowering agents, ACE inhibitors, low-molecular-weight heparin, antioxidants, and somatostatin analogues. One metanalysis suggest that calcium channel blockers and fish oil had beneficial effects on restenosis after PTCA (Figure-4). However, the randomized CART trial did not demonstrate a benefit for fish oil, and initial excitement for calcium channel blockers was tempered by negative
reports from several randomized trials. **Amilodipin** (10 mg/d for 2 weeks prior and 4 weeks after PTCA) decreased ischemic complications at 4 months but failed to reduce restenosis in the randomized CAPARES trail. Small randomized trials of **cilostazol**, phosphodiesterase III inhibitor used for claudication, have shown reductions in restenosis after PTCA and stenting, further trials are pending. **HMG-Co-A reductase inhibitors (Statins)** have several potential mechanisms of action that could decrease restenosis, although studies thus far have been disappointing. Two randomized trials suggest that **abciximab** and **angiopeptin (Somatostatin analog)** significantly decreased clinical restenosis after PTCA, however, quantitative volumetric ultrasound analysis after stenting failed to show a reduction in initial hyperplasia with abciximab, and there was no difference in angiographic restenosis in the angiopeptin trial. **Probucol**, given one month prior to PTCA and continued for at least 6 months, showed benefit in two randomized studies, but pretreatment for one month is impractical in most patients. Data from TREAT and TREAT-2 suggest a possible benefit effect for tranilast after angioplasty. Despite initial promise, **trapidil** failed to decrease restenosis in the randomized TRAPIST study. Trials of local delivery of **alcohol** and other **anti-proliferatives** show early promise, but to date, no pharmacologic therapy has clearly been shown to reduce restenosis. Because of the differing mechanisms of restenosis after PTCA and stenting, conclusions of efficacy after PTCA do not necessarily apply to stenting [45].

**B-Mechanical Interventions** [44]: The **stent** is the only device that has been shown to reduce the incidence of restenosis compared to PTCA. Randomized trials (STRESS, BENESTENT) have conclusively demonstrated a decrease in restenosis for **de novo lesions** in native coronary arteries. In addition, multiple observational studies strongly suggest lower restenosis rates for stents in saphenous vein grafts.
Results of the randomized SAVED trial (Stenting or Angiography in Vein Graft Disease) found that stents reduced clinical (but not angiographic) restenosis when compared to PTCA alone. Other atheroablative devices have been disappointing for preventing restenosis. In ERBAC, despite a larger post-procedural lumen diameter, restenosis rates were higher after Rotablator and excimer laser compared to PTCA. Studies of directional atherectomy (OARS, BOAT) reported less angiographic restenosis vessel revascularization or major adverse cardiac events.

**C-Radiation Therapy** [45]: Limited data suggest a potential role for radiation therapy in the prevention of restenosis following balloon angioplasty in previously untreated coronary arteries. **Beta-radiation** reduced target lesion revascularization (6% vs. 24%, $P < 0.05$) and restenosis (8% vs. 39%, $P = 0.012$) in PREVENT and low restenosis rates (15% and 4%) were achieved in two other studies. In a dose ranging study of beta-radiation after PTCA (without stents), restenosis rates after 9-Gy,
15-Gy, and 18 Gy were 28.1%, 16.7%, and 3.9% respectively. Patients receiving a stent had more thrombosis or late occlusion than patients treated by PTCA alone (14.3% vs. 3.3%). Results of other randomized trials are pending.

1.6.2. Management of restenosis after PTCA:
The management of patients with restenosis depends on patient characteristics, myocardium at risk, lesion morphology, extent of coexisting coronary artery disease, and LV function. Repeat PTCA can be performed with high procedural success > 95% and low complication rates < 3-5%, and is frequently the procedural of choice for focal restenosis after stenting. Early registry data suggested higher restenosis rates for stenting of restenotic lesions compared to de novo lesions, which has been confirmed in late studies. More recently, however, compared to patients with restenotic lesions treated by PTCA, those treated by stenting had fewer late cardiac events (4.8% vs. 20%). Directional atherectomy can be used to treat restenosis after PTCA, but restenosis rates tend to be higher for restenotic compared to de novo lesions. In a study of 1,087 restenotic lesions treated by PTCA, directional coronary atherectomy (DCA) or stents, procedural success was achieved in 94-96% despite better initial lumen enlargement for DCA and stents, in-hospital complications, recurrent restenosis, and 3-year event-free survival were similar for all 3 devices [45].

1.6.3. Treatment of In-stent restenosis (Table-4):

A-Angioplasty, Debulking, and Restenting: IVUS studies demonstrated that PTCA for stent restenosis provided additional stent expansion and tissue extrusion out of the stent, accounting for 56% and 44% of net gain, respectively. PTCA did not achieve the same dimensions as original stent because of re-intrusion of intimal tissue. The combination of debulking (Rotablator, DCA, or Laser) and adjunctive PTCA may not have benefit over PTCA alone, despite initially promising results. In the large, randomized ARTIST trial, Rotablator for diffuse stent restenosis was
associated with higher in-lab complications, more late clinical events, and smaller dimensions at 6 months compared to PTCA alone, but in ROSTER, 6-month TLR was lower after Rotablator.

A metanalysis of PTCA, DCA, Rotablator, Laser, and restenting for stent restenosis reported a 6-month TLR of 30% regardless of the device. Although IVUS studies suggest that restenting eliminates intimal reintusion associated with PTCA and other devices, this effect is not sufficient to prevent recurrent restenosis. Registries of small numbers of patients with in-stent restenosis treated by drug-eluting stents indicate excellent results using Sirolimus- or Paclitaxel-eluting stents [45].

**B- Ionizing Radiation:** At the present time, no pharmacologic or mechanical intervention can reliably treat stent restenosis. However, brachytherapy holds real promise for inhibiting intimal proliferation and decreasing the incidence of stent restenosis [45].

**C – Drug eluting Stents:** I will discuss it in details in the next chapter.

Table-4. Treatment strategies for stent restenosis.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanical Approaches</strong></td>
<td></td>
</tr>
<tr>
<td>- PTCA</td>
<td>- Success rates exceed 90%, restenosis rates vary from 30-80% depending on pattern of stent restenosis and nature of target lesion.</td>
</tr>
<tr>
<td>- Debulking (DCA; Rotablator, Laser)</td>
<td>- Despite initial enthusiasm, randomized trials show no benefit compared to PTCA.</td>
</tr>
<tr>
<td>- Stenting</td>
<td>- Achieves the best immediate angiographic results, long-term outcomes are uncertain.</td>
</tr>
<tr>
<td>- Cutting Balloon</td>
<td>- May facilitate immediate lumen enlargement but further study is needed.</td>
</tr>
</tbody>
</table>
1.7. Coated Stents for the Prevention of Restenosis:

Increasing focus has recently been directed towards the different parameters of drug-eluting stents—stent design, stent coating, and drug selection—and the manner in which each of these elements may affect the function of the stents. The final parameter that bears consideration in complete evaluation of drug-eluting stents is the disease state of the target vessel.

Several specific characteristics of design may affect restenosis, although design optimization often presents a choice between acute procedural success and long-term biological stability. The influence of design parameters such as strut thickness and cell configuration is described [41,42].

1.7.1. Stent design:

Development in stent strut configuration, strut thickness, and delivery-balloon technology have resulted in important procedural attributes, including reduced device profiles, increased flexibility and conformability, and fluoroscopic visibility. The same refinements that have led metal-stent design to this level have also limited
restenosis, with rates from recent clinical studies in the 10%-20% range [41]. Recent clinical studies suggesting an impact of metal-stent design on coronary restenosis have a foundation in several animal studies that established a link between design and depth of injury, and subsequent neointimal thickening or experimental restenosis [41,42]. Several specific design parameters may affect restenosis, although design optimization often presents a choice between acute functionality and long-term biological stability. For example, stents with thinner struts may have less visibility but also have more favorable flow dynamics within the lumen, providing less turbulent flow and less corresponding platelet activation and inflammatory cell recruitment [40]. Current metal stents can be categorized into “closed-cell” and “open-cell” configurations. Closed-cell stents have cells whose bounded area does not change as the stent is flexed (a diamond shape is an example of a close cell), while open-cell stents have cells that grow in area as the stent is flexed (a coil spring is an example). Stent with an “open-cell” configuration tend to have greater conformability to curved segments after expansion, but therefore have greater variations in arterial surface coverage between the inner and outer curvatures of a tortuous segment than do stents with a “closed-cell” design. Similarly, stents with greater surface coverage offer greater luminal circularity, minimizing tissue growth as the vessel remodels to regain optimal flow characteristics [17], but at the same time have the potential to be rigid and non-conformable and to afford limited access to side branches. Overall, in the current era, competing aspects of stent design allow practitioners to choose stents specific to the needs and challenges of a given lesion. That is, in a straight, large vessel without involved side branches, a fairly rigid but high-surface-coverage stent can be used, whereas in a smaller vessel with tortuously or side-branches involvement, a more
flexible stent with larger openings between struts may be the better option, albeit the expense of lower surface coverage and perhaps slightly restenosis rates.

1.7.2. Drug Coating:

Recently, novel local delivery systems using coated stent technologies that elute potent anti-proliferative agents resulted in another dramatic reduction in restenosis rates, with rates now less than 10% in short-term follow-up. This success has resulted from largely empiric selection of drug, using anti-neoplastic and immunosuppressant agents [49].

A general understanding of cell cycle kinetics is important for designing anti-proliferative agents to inhibit neointimal growth (desirable effect) rather than killing local cells directly (undesirable effect). The two salient cell cycle effects of drugs known since the 1960’s are cell cycle arrest (the cytostatic effect) and cell killing (the cytotoxic effect) [48]. Many of the most potent cytotoxic agents act by damaging DNA, with cell killing or cytotoxic potential greater during S-phase when DNA synthesis occurs. Agents that block the mitotic spindle formation (during M-phase) have activity against rapidly dividing cells, as occurs during neointimal growth. Thus, knowledge of cell cycle details and the agent primary action and dose help determine when cytotoxic rather than cytostatic effects occur. This knowledge is critical to designing drug regimens that effectively inhibit cellular proliferation (cytostatic) rather than cell killing [49].

Stent coating can be passive or active coating. While passive coatings serve good biocompatibility, active coatings directly influence the intima proliferation. Active coatings are generally based on the effect of drug. They are either directly bonded to the surface of the stent or trapped in the three-dimensional polymers, which act like a sponge. However, the presence of polymer itself may lead to delayed inflammation and proliferation causing restenosis. Currently there are three different
approaches of binding drugs to coronary stents [26,63]:

1- **Drug binding by means of a polymer on the surface of stent.**
2- **Drug binding aided by inorganic stent coating.**
3- **Direct drug binding upon the stent surface without coating.**

On the basis of the mechanism of action of the biological compound and its target in the restenotic process, drug-eluting stents may be generally classified as immunosuppressive, antiproliferative, anti-inflammatory, antithrombotic, and pro-healing. Some agents, such as sirolimus, may affect multiple targets in the restenotic process (Figure-5) [56]. Currently, the two most successful drugs used on coated stents today are rapamycin and paclitaxel. Each is a potent proliferative inhibitor, and is cytostatic rather than cytotoxic at the concentrations used in stents. Paclitaxel at higher concentrations is cytotoxic, as evidenced by use in malignancies. To build on these first generation successes and improve drug development, critical understanding of these two agents is useful [48].

1.7.3. **Sirolimus-Eluting Stents:**

■ **Mechanism of Action:**

Sirolimus (rapamycin) was discovered in a soil sample from Easter Island (known locally as Rapa Nui). A naturally occurring product that is isolated from *Streptomyces hygroscopicus*, sirolimus is an extremely lipophilic macrolide that was initially developed as an *antifungal agent* on the basis of its ability to inhibit the growth of yeast. However, sirolimus was quickly observed to have potent immunosuppressive activity in mammals, which put a halt to its development as an antibiotic. In 1988, efforts to develop sirolimus as an *immunosuppressant agent* were renewed. These efforts ultimately led to approval by the Food and Drug Administration (FAD) of use of sirolimus as an immunosuppressant agent in September 1999 for the prophylactic treatment of renal transplant rejection.
Figure 5. Leading processes of restenosis (solid lines) and correspondent inhibitory (dashed lines) effects of different biological agents. MMP = Matrix Metalloproteinase, VEGF = Vascular Endothelial Growth Factor.

Evidence emerged in the early to mid-1990s that sirolimus was a potent inhibitor of the proliferation of VSMC, and the idea that it could be used to inhibit coronary artery restenosis was hatched. Study showing that sirolimus also inhibits the migration of VSMC, providing further impetus to promote the development of the drug for the...
prevention of both in-stent restenosis and accelerated arteriopathy after heart transplantation, because the proliferation and migration of VSMC have a central role in both of these processes [29,30].

Sirolimus, with a molecular weight of 914, is a 31-member macrocyclic lactone that is structurally similar to the anti-fungal immunosuppressant tacrolimus, a 23-member macrocyclic lactone that is also produced by a streptomyces species. Oral sirolimus has a long half-life (approximately 63 hours), is largely (about 90%) sequestrated in erythrocytes, resulting in higher concentrations in whole blood than in plasma, and is metabolized by the 3A isoform of cytochrome P-450. Its primary route of elimination is through the biliary-fecal pathway [29]. The major intracellular sirolimus receptor is a small, ubiquitous, 12-kD protein called *FK506-binding protein (FKBP 12)*, which is a member of the immunophilin family of cytosolic binding proteins. Rapamycin-FKBP 12 inhibits a kinase called the mammalian target of rapamycin (*mTOR*) is a large conserved member of the phosphatidylinositol kinas (PIK) related kinase family protein that regulates protein translation, cell cycle progression, and cell proliferation. mTOR is a critical and essential regulator of many second messenger pathway within eukaryotic cells.

Rapamycin enters cells easily where it is bound to a specific intracellular receptor FKBP 12, rapamycin/FKBP 12 complex is a highly specific inhibitor of mTOR (Figure-6). Growth factor activation of cells activates the kinas activity of mTOR, using a number of classical intracellular signaling systems, including PI-3 kinase and the serine theonine kinase Akt. mTOR, together with PI-3K dependent signals phosphorylates down-stream effectors, the best characterized of which are p70 S6 (S6K1) and 4EBP-1. S6 kinase directly phosphorylates the 40S ribosomal protein S6, which correlates with increased translation of sequences that encode components of the translational machinery.
Figure-6. The effect of rapamycin is mediated via binding to a specific intracellular receptor, FKBP 12, with subsequent inactivation of the enzyme mTOR, and reduced activity of mTOR targets including S6 kinase and 4EP-1.


Phosphorylation of the translational repressor 4EBP-1 leads to increased cap dependent translation through eukaryotic initiation factor (eIF) 4E-F. Thus, rapamycin inhibits protein synthesis. S6 kinase also phosphorylates many other downstream proteins, such as CBP80 (functions in RNA export and spicing). Growth factor activation of cells also down-regulates the cyclin dependent kinase inhibitor (CDKI)
p27, in addition to increasing expressing of cyclins, predominately cyclin D and E, these events are required for transit of the G1 cell cycle restriction point controlled by the retinoblastoma protein RB (Figure-7).

Figure-7. Artery injury induces growth factor release, resulting in increased expression of CDK 2 and 4, down-regulation of p27, with resultant increased activity of CDK 2/cyclin E and CDK 4/cyclin D complexes. These enzymes phosphorylate (inactivate) pRB allowing passage of cells from G1 into S phase, with subsequent cell division. Rapamycin leads to failure to down-regulate p27, reduced CDK 2 and 4 activities, and failure to inactivate RB, with subsequent arrest in G0/G1.


RB is a nuclear phosphoprotein that arrests the cells during the G1 phase of the cell cycle by repressing transcription of genes required for the translation from G1 to S phase. A major cellular target of pRB is the E2F family of transcription factors. Progression of a cell through G1 and S phase requires inactivation of pRB by phosphorylation. This is carried out by cyclin-dependent kinases with their cyclin
partners. Binding of the pRB to the E2F transcriptional factor prevents E2F transcriptional activity. As CDK activity increases, pRB becomes more phosphorylated, resulting in the release of E2F from pRB. This entire process in turn activates the S phase genes [29, 30, 31, 38].

**Pre-clinical Data:**

The sirolimus-eluting stent is composed of a tubular stainless steel stent, the Bx Velocity stent (Cordis), coated with a 5-µg-thick layer of nonerodable polymer blended with sirolimus in a concentration of 140 µg sirolimus/cm2 of stent. The release kinetics can be modulated in such a way that both fast-release (< 15-day drug release) and slow-release formulations (> 28-day drug release) are obtained [55].

Suzuki et al. investigated the efficacy of this agent at inhibiting neointimal hyperplasia in the porcine model [58]. Stents were coated with a nonerodable polymer containing 185 µg sirolimus (SRL), 350 µg Dexametasone (DEX), or 185 µg SRL and 350 µg DEX along with uncoated controls. Forty-seven stents (metal n=13, SRL n=13, DEX n =13, SRL and DEX n =8) were inserted in major coronary arteries of 16 pigs after overstretch injury. Histological analysis and quantitative coronary angiography (QCA) at 28 days revealed highly significant reductions in inflammation, neointimal area, and percent area stenosis between sirolimus-coated stents and uncoated stents. There was no difference in the above variables between the stents coated only with dexamethasone and the controls. Klugherz et al. also demonstrated inhibition of neointimal hyperplasia by sirolimus-coated stents in rabbits. This inhibition appeared to be dose-dependent [1, 54]. These studies show that sirolimus-eluting stent causes a short-term reduction in neointimal hyperplasia in animal models.
Clinical Data: De Novo Lesion

**A - FIM Study:** The First In Man (FIM) study was the first published nonrandomized study in humans to investigate stent coated with antimitotic agents. It was conducted jointly in Brazil and Europe to assess the efficacy of sirolimus-coated stents in inhibiting neointimal hyperplasia. The patients had quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) done at 4 months, with clinical follow-up at 8 months. No patients had binary restenosis shown by QCA, and all patients had < 20% diameter stenosis by IVUS. No major adverse cardiac events (MACE) had occurred by 8 months. There was also no difference in clinical or angiographic endpoints between the fast-release and slow-release formulations. The 1-year follow-up results of this cohort have also published, showing essentially unchanged QCA variables. Only 1 MACE occurred by 15-month clinical follow-up [2, 40, 56].

The combination Brazilian and European results of the FIM study show no binary restenosis and no MACE up to 12 months, suggesting that both fast-release and slow-release sirolimus-coated stent have a potent inhibitory effect on neointimal hyperplasia in humans [27, 56].

**B – RAVEL Study:** RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions Trial (RAVEL), led by Marie-Claude Morice, was a natural extension of the Cypher experience. RAVEL was a double-blind randomized trial in 238 patients with simple de novo lesions in 19 clinical centers from Europe and Latin America [27, 52]. The primary endpoint was in-stent late luminal loss. Patients received clopidogrel or ticlopidine for 2 months. In-stent late loss was significantly lower in the sirolimus stent group (- 0.01 mm) than in the standard stent group (0.80 mm, P < 0.001). None of the patients in the sirolimus-stent group had binary restenosis, and the incidence of MACE was 5.8% in the sirolimus-stent group after 1 year. Notably, no episodes
of stent thrombosis occurred. This study uniquely zero percent restenosis after coronary stenting [39, 52, 55].

**C – SIRIUS Study (United States):** Data from the multicenter, randomized, double-blind study of the SIRolImUS-coated Bx Velocity-stent in the treatment of patients with de novo coronary artery lesions (SIRIUS) have recently been presented. Patients (n = 1058) with de novo lesions were randomized to receive sirolimus-coated stents or bare Bx Velocity stents at 53 US sites [54]. The primary endpoint was target vessel failure, which included cardiac death, myocardial infarction, or target vessel revascularization at 9 months, and secondary endpoint included patient subsets with angiographic and IVUS follow-up. The Cypher stent was safe with an overall stent thrombosis frequency of 0.04%. In these more complex patients and lesions, Cypher was still associated with striking > 90% reduction of neointimal hyperplasia within the stent assessed by IVUS. Angiographic outcomes were also markedly improved with 70–80% reductions in late loss and restenosis [27, 29]. Clinical outcomes in SIRIUS were also markedly improved, especially the reduction in out-of-hospital TLR at 9-month follow-up. The primary endpoint, TVF, was reduced by 59%, from 21% with control bare stents to 8.6% with Cypher stents.

**D – The New (E + C) SIRIUS (Europe and Canada) Trials:** Building on the US SIRIUS experience, 2 additional clinical trials were simultaneously begun in Europe (E-SIRIUS) and Canada (C-SIRIUS). The E-SIRIUS study involved 352 patients from 35 European sites. The C-SIRIUS study involved 100 patients from 8 sites. Both E-SIRIUS and C-SIRIUS were double-blinded, randomized clinical trials comparing the Cypher stent vs. bare stent controls and both had identical inclusion criteria and follow-up endpoints [27]. In some respects the New SIRIUS patients were more complex than the US SIRIUS patients, with smaller vessels and longer lesions treated (Table-5).
Despite the more complex lesions in New SIRIUS, the 8-month angiographic outcomes (late loss and restenosis) and the 9-month clinical outcomes (TLR, TVR, TVF, and MACE) showed even greater improvement with Cypher compared with control bare stents [27].

Table-5. Comparison of study variables.

<table>
<thead>
<tr>
<th></th>
<th>US SIRIUS (n=1058)</th>
<th>New SIRIUS (n=452)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (%)</td>
<td>26.4</td>
<td>23.3</td>
</tr>
<tr>
<td>Reference Diameter (mm)</td>
<td>2.80</td>
<td>2.57</td>
</tr>
<tr>
<td>Lesion Length (mm)</td>
<td>14.4</td>
<td>14.7</td>
</tr>
<tr>
<td>Stent/Lesion Length Ratio</td>
<td>1.6</td>
<td>1.7</td>
</tr>
</tbody>
</table>


Clinical Data: In-Stent Restenosis

The in-stent restenosis registry involved 41 patients treated in Brazil (n=25) and in the Netherlands (n=16). This was an open-lable safety study involving only patients with single-vessel in-stent restenotic lesions. The protocol allowed the implantation of up to 2 Cypher stents. In the Brazilian cohort, all vessels were patent at the time of 12-month follow-up angiography. Late loss averaged 0.36 ± 0.46 mm in-stent and 0.16 ± 0.42 mm in-lesion. One of the 25 patients developed in-stent restenosis by 1-year follow-up. There were no deaths, stent thrombosis, or repeat revascularization. The Rotterdam cohort included a more complex group of patients. In this group, 19% of the patients had previous brachytherapy failure, and 1 heart transplantation was treated. There were 2 deaths, 1 late thrombosis, 1 vessel occlusion, and 2 in-lesion restenosis [1]

1.7.4. Paclitaxel-Eluting Stents:

Mechanism of Action:

Paclitaxel was isolated from the bark of the Pacific Yew, Taxus brevifolia, in 1967 by U.S. National Cancer Institute (NCI) in an effort to screen naturally occurring anti-neoplastic agents. Interest in this compound was accelerated once its unique
mechanism of action was characterized and the potential for this drug to inhibit
cellular hyperplasia was postulated. Paclitaxel was introduced as the active
ingredient to Taxol, one of the most successful chemotherapeutic agents to date [21, 45]. Paclitaxel has a unique mechanism of action differentiating it from other micro-
tubular agents in that it promotes the assembly (polymerization) of tubulin into stable
microtubules. Cells treated with paclitaxel will form unusually stable microtubules,
which in turn stabilize the micro-tubular dependent activities of cell. Micro-tubules
reside in the cytoplasm of all eukaryotic cells contributing to make-up of the
cytoskeleton. Micro-tubules only formed when their function is elicited, otherwise they
reside
in the cytoplasm as sub-units called tubulin. Tubulin and micro-tubules exit in
a dynamic equilibrium shifting from one state to the other depending on cellular
needs [4, 44, 45].

Micro-tubules are necessary for the function and structure of normal active cells, and
are best known for their contribution to the mitotic spindle during mitosis. They play
an active role in the cell cytoplasm to facilitate cell shape, cell movement and
intracellular transport. More specifically, micro-tubules are essential to:

1- **Cellular division.**

2- **Cell motility / migration.**

3- **Intracellular signaling (signal transduction).**

4- **Extra-cellular secretory processes.**
Micro-tubules disassembly is required for G2 transition into M phase, the drug thus blocks cell proliferation in G2/M. Paclitaxel has shown a number of effects including: reduction of inflammation, interference with cell migration, anti-proliferative, apoptotic, and necrotic effects on cells depending on the dose delivered [20, 44]. This may be most easily depicted in Figure-8. Several researchers have noted the different effects of paclitaxel on cell lines in a dose dependent fashion. Belotti et al. [5] noted the inhibition of cell migration at lower paclitaxel concentration (10-900 fold) than those required to affect cell proliferation. Carbal et al. [4] found that different cell types were more sensitive to paclitaxel than others. They theorized that cells with high levels of polymerized tubulin, such as macrophages, would be more sensitive to paclitaxel than other cells. They theorized that this maybe the mechanism by which inflammatory cells (macrophages) and SMCs are more sensitive to paclitaxel than ECs.


- **Pre-clinical Data:**

  Unlike other anti-mitotic agents, paclitaxel shifts the cytoskeleton equilibrium toward assembly, leading to reduced vascular cell proliferation, migration, and
signal transduction. Paclitaxel is highly lipophilic, resulting in a rapid cellular uptake and long-lasting effect in the cell [54]. Encouraging results have been reported in several animal studies investigating paclitaxel-coated stents. These studies have demonstrated reduction of neointimal hyperplasia of up to 60% when compared with controls in the rabbit iliac artery and porcine coronary artery models. The inhibitory effect appears to be dose-dependent. However, arteries treated with paclitaxel showed incomplete healing, late persistence of large number of macrophages, and fibrin deposition [25].

Similar findings were observed with a stent platform coated with cross-linked biodegradable polymer (chondrition sulfate and gelatin) and 42.0, 20.2, 8.6, or 1.5 µg of paclitaxel in rabbit iliac arteries [13, 56].

■ Clinical Data: Polymer-Based Paclitaxel-Eluting Stents

A series of clinical trials (TAXUS I through VI) have been designed to test the feasibility and effectiveness of polymer-based Paclitaxel-eluting stents in a variety of clinical settings [56].

1 – TAXUS I: The TAXUS I trial was the first in-human experience evaluating safety and feasibility of the TAXUS NIRx stent system – loaded with 85 µg of paclitaxel (1.0 µg/mm2) - compared with bare NIR stents (control) (Bosten Scientific Corp) for the treatment of coronary lesions. This trial was a prospective, double-blind, three-center study randomizing 61 patients with de novo lesion (≤ 12 mm) to receive TAXUS (n=31) versus control (n=30) stents (diameter 3.0 or 3.5 mm). The 30-day major adverse cardiac event (MACE) rate was 0% in both groups (P = NS). No stent thromboses were reported at 1, 6, 9, or 12 months. At 12 months, the MACE rate was 3% (1 event) in the TAXUS group and 10% (4 events in 3 patients) in control group(P = NS) (Table-17). Six-month angiographic restenosis rates were 0% for TAXUS vs. 10% for control (P = NS). There were significant improvements in MLD
(2.60 ± 0.49 vs. 2.19 ± 0.65 mm), DS (13.56 ± 11.77 vs. 27.23 ± 16.69), and late loss 
(0.36 ± 0.48 vs. 0.71± 0.48 mm) in the TAXUS group (all P < 0.01) [18]. No evidence 
of edge restenosis was seen in either group. Intravascular ultrasound analysis 
showed significant improvement in normalized neointimal hyperplasia in the TAXUS 
(14.8 mm3) group compared with the control group (21.6 mm3) (P < 0.05). In this trial, the TAXUS slow-release stent was well- tolerated and showed promise for treatment of coronary lesions, with significant reduction in angiographic and intravascular measures of restenosis [19].

2 – TAXUS II: This triple-blinded, randomized, multi-center trial tested the efficacy of 2 formulations of paclitaxel-eluting NIRx Conformer stent to treat patients with short de novo coronary lesions. The study included 536 patients divided into 4 groups: 267 were treated with either bare (n=136) or slow-release (SR, n=131) eluting stents, whereas 269 were treated with bare (n=134) or moderate-release (MR, n=135) eluting stents. All cohort were treated with a 15-mm NIRx Conformer Stent. All eluting stents were coated with the translute polymer loaded with 1 µg of paxlitaxel/mm2. Clopidogrel (75 mg) was administrated for 6 months. The primary endpoint was 6-month percent in-stent net volume obstruction measured by IVUS. Secondary endpoints were 6-month angiographic restenosis and 6- and 12-month incidence of MACE, a composite of cardiac death, myocardial infarction, and repeat revascularization. At 6 months, percent net volume obstruction within the stent was significantly lower for TAXUS stents (7.9% SR and 7.8% MR) than for respective controls (32.2% and 20.5%; P < 0.0001 for both) (Figure-9). This corresponded with a reduction in angiographic restenosis from 17.9% to 2.3% in the SR cohort (P <0.0001) and from 20.2% to 4.7% in the MR cohort (P=0.0002). Late loss was 0.31 mm (SR) and 0.30 mm (MR) in the eluting-stent groups.
The incidence of MACE at 12 months was significantly lower (P=0.0192) in the TAXUS-SR (10.9%) and TAXUS-MR (9.9%) groups than in controls (22.0% and 21.4%, respectively), predominantly because of a significant reduction in repeat revascularization of the target lesion in TAXUS-treated patients [10].


**3 – TAXUS III:** This trial was performed to evaluate the feasibility and safety of paclitaxel-eluting stent for the treatment of in-stent restenosis (ISR) and was conducted at 2 sites in Europe, enrolling 28 patients with ISR meeting the criteria of lesion length ≤ 30 mm, 50% to 90% diameter stenosis, and vessel diameter 3.0 to 3.5 mm. They were treated with one or more TAXUS NIRx paclitaxel-eluting stents. Twenty-five patients completed the angiographic follow-up at 6 months, and 17 of these underwent IVUS examination. No sub-acute stent thrombosis occurred up to 12 months, but there was one late chronic total occlusion, and additional 3 patients showed angiographic restenosis. The mean late loss was 0.54 mm, with neointimal
hyperplasia volume of 20.3 mm³. The major adverse cardiac event rate was 29% (8 patients; 1 non-Q wave MI, 1 CABG, and 6 TLR). Of the patients with TLR, 1 had restenosis in a bare stent implanted for edge dissection and 2 had restenosis in a gap between 2 paclitaxel-eluting stents. Two patients without angiographic restenosis underwent TLR as a result of the IVUS assessment at follow-up (1 incomplete apposition and 1 insufficient expansion of the stent). Overall binary restenosis rate was 16% (4 of 25) [59].

4 – TAXUS IV: TAXUS IV, a prospective, double-blind, controlled randomized trial of 1326 patients study, was conducted to evaluate the safety and efficacy of the slow-release, polymer-eluting TAXUS stent on restenosis following coronary artery stenting. The trial enrolled 1326 patients at 73 sites. Principle inclusion criteria were de novo coronary lesions 10-28 mm long, in native coronary vessels with an RVD of 2.5 to 3.75 mm, and coverable with a single 16, 24, or 32 mm stent. The primary endpoint was 9 month TVR. An angiographic analysis was conducted at the 9-month follow-up in a subset of 732 patients. The angiographic subset was further stratified to analyze patients with medically treated diabetes (n=318), and patients with RVD < 2.5 mm (n=415). Both treatment groups were well matched for all measured baseline demographic and lesion characteristics. For the angiographic subset, mean lesion length was 14.4 mm for treatment group A and 14.4 mm for treatment group B. Baseline values for RVD were 2.76 and 2.80 mm for groups A and B respectively, as compared to post-procedure values of 2.79 and 2.83 mm. In-lesional MLD was 0.93 and 0.95 mm for groups A and B respectively at baseline. Post-procedure in-stent MLD was 2.65 and 2.67 mm and analysis segment MLD was 2.26 and 2.29 mm respectively for groups A and B [12].
Clinical Data: Non-Polymer-Based Paclitaxel-Eluting Stents

1- ASPECT Trial: Asian Paclitaxel-Eluting Clinical Trial was randomized study compared Supra-G stents (Cook) directly impregnated with 2 different doses of paclitaxel (1.3 µg and 3.1 µg/mm2) versus bare metal stents. At 6-months, the angiographic parameters of percent diameter stenosis (14 ± 21% vs. 39 ± 27%) and binary restenosis (4% vs. 27%) were both decreased significantly in the high-dose group compared with the uncoated stents (P < 0.001) [34]. In-stent late loss was 0.29 mm in the high-dose group, compared with 0.57 mm in low-dose group and 1.04 mm in the bare stent group. Overall, 1-year MACE incidence and target lesion revascularization rates were similar among all groups. However, 4 of the 12 patients receiving the high-dose eluting stent had stent thromboses [37].

2 – ELUTES (European Evaluation of Paclitaxel-Eluting Stent): This trial compared the V-Flex stent (Cook) loaded with 4 different doses of paclitaxel (0.2, 0.7, 1.4, and 2.7 µg/mm2) versus bare metal stents for the treatment of de novo lesions. Stents were directly impregnated with paclitaxel without a polymer. Patients (n=180) were randomized evenly among the 5 groups. A dose-dependent effect on in-stent late loss was observed: 0.1 mm in the high-dose groups, and 0.7 mm in both low-dose and control groups. One-year MACE incidence was similar among groups. There were no reports of death or stent thromboses [56].
2- Methods:

2.1. Patient Population:

This observational study was conducted in the department of Cardiology at the University of Essen, Germany. A total of 106 consecutive patients received either Cypher stent or Paclitaxel stent and underwent angiographic follow-up between Aug 2002 and Feb 2004.

The patients were divided into two groups (Cypher, n=54; Paclitaxel, n=52). Age of patients was 61±10 years of Cypher group versus 59 ±11 years of Paclitaxel group. The Cypher group consisted of 41 male (76%) and 13 female patients (24%), whereas Paclitaxel group consisted of 37 male (71.2%) and 15 female patients (28.8%). Lesions were either de novo lesions (Cypher, n=40; Paclitaxel, n=30) or restenotic lesions (Cypher, n=14;Paclitaxel, n=22). Patients in the Cypher group underwent angiographic follow-up after 4-10 months (6.40 ±1.47months), whereas the follow-up duration in the Paclitaxel group was 3-11 months (6.38 ± 2.43 months). There was statistical difference in follow-up duration.

Patients were classified as hypertensive when they had a documented history of hypertension, used blood pressure lowering drugs, or if repeated systolic and diastolic blood pressure measurements exceeded 140/90 mmHg. Patients were classified as hypercholesterolemic if serum cholesterol values exceeded 5.2 mmol/L, or if the individual received cholesterol-lowering drugs. Patients were classified as diabetic when patient received anti-diabetic drugs, or if fasting blood glucose exceeded 6.9 mmol/L. Obesity was defined as body mass index > 25 kg/m².

A positive Family history was defined as presence of coronary artery disease in first-degree relatives of patients before 55 year of age.
Smoking was defined either as previous smoking or as current smoking (within the month before intervention).

See figure-10 which shows study design.

**Primary endpoint:** Angiographic DS% at follow-up.

**Angiographic endpoints:** Late loss, binary restenosis, and MLD at follow-up.

**Clinical endpoints:** The rate of death, MI (Q-wave, and non-Q-wave), CABG, TLR, and TVR at follow-up.

**Figure-10. Study design. RVD: Reference vessel diameter.**

### 2.2. Procedure:

Selective coronary angiography was performed by the Judkins technique using the BICOR system (Siemens, Erlangen). Following femoral sheath insertion, all patients received 10,000 IU of heparin. In addition, 0.2 mg nitroglycerin was given intra-coronary after engagement of the left main stem and the right coronary artery. At least four projections for the left coronary artery and two projections for the right
coronary artery were taken for optimal views. Guiding catheters were either 6F or 8F (Cordis, Miami, FL, USA). The stents used in the study were sirolimius-eluting Bx Velocity balloon-expandable stent (Cordis Corp) in 2.5, 3.0, and 3.5 mm diameter, and V-Flex stent (Cook, Inc) in 2.5, 3.0, and 3.5 mm diameter.

Standard angioplasty and stent placement were performed with a monorail technique. The stents were chosen to achieve a stent-to-artery ratio of approximately 1.1:1.0. See table-6 which shows characteristics of stents in both groups.

All patients received aspirin 100 mg and clopidogrel 300 mg loading dose before the procedure. Heparin was administered during the procedure according to standard practice. After the procedure, in addition to aspirin 100 mg indefinitely, clopidogrel 75 mg/d was recommended for 6 months.

**Table-6. Characteristics of stents in the both groups.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cypher group (n=54)</th>
<th>Paclitaxel group (n=52)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of Stents</td>
<td>86</td>
<td>82</td>
<td>0.60</td>
</tr>
<tr>
<td>One stent</td>
<td>31</td>
<td>28</td>
<td>0.52</td>
</tr>
<tr>
<td>Two stents</td>
<td>14</td>
<td>18</td>
<td>0.32</td>
</tr>
<tr>
<td>Three stents</td>
<td>9</td>
<td>6</td>
<td>0.21</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>14 ± 4.8</td>
<td>17.5 ± 4.7</td>
<td>0.0002</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3.0 ± 0.9</td>
<td>3.10 ± 0.31</td>
<td>0.22</td>
</tr>
<tr>
<td>Inflation pressure (atm)</td>
<td>16 ± 2.4</td>
<td>15 ± 1.9</td>
<td>0.31</td>
</tr>
<tr>
<td>Direct stenting – no (%)</td>
<td>36 (66.6)</td>
<td>30 (57.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>Post-dilatation – no (%)</td>
<td>6 (11.1)</td>
<td>16 (30.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
2.3. Angiographic Analysis:

Coronary angiograms were obtained before and after stent implantation and at follow-up. All angiograms were done and analyzed by our department of Cardiology.

Quantitative coronary angiography (QCA) was performed off-line with the use of the edge detection system (Cardiovascular measurement system, Medis medical imaging system, Leiden, the Netherlands). With this system, the mean variation in determining the absolute diameter is ≤ 0.13 mm [22]. For calibration, the contrast filled guiding catheter was used.

Angiography was carried out in the same orthogonal views before and after intervention and at follow-up. All angiograms were evaluated after the administration of intracoronary nitrates. The area of interest was selected after reviewing all cine-films performed during the index procedure. The normal diameter proximal and distal to the lesion were used to interpolate the reference diameter.

The electrocardiographic tracing was also displayed in any angiographic sequence to select frames in the same cardiac cycles. A diastolic frame with sharply defined edges without foreshortening and overlap was usually selected for quantitative coronary angiography.

From orthogonal views, the minimal luminal diameter, the reference diameter, and the percentage of stenosis were calculated. Coronary luminal diameter and degree of stenosis were measured before and after intervention, and at follow-up. In addition, acute gain and late loss were calculated (Figure-11).

Restenosis was defined as > 50% diameter stenosis at follow-up. The late loss was defined as the diameter immediately after the procedure minus the diameter at follow-up.
**Acute gain** was defined as the diameter immediately after the procedure minus the reference diameter immediately before the procedure.

![Image](image-url)

**Figure-11. Example from our patients shows high-degree stenosis by using automated edge-detection of our quantitative coronary angiography system.**

**Loss index** was defined as the late loss divided by acute gain. **Net gain** was defined as the diameter at follow-up minus the diameter before the procedure.

The **target lesion (TL)** was defined as the stent segment plus 5 mm proximal and 5 mm distal to the edge of the stent. The **vessel segment (VS)** was defined as the segment bounded by side branches proximal and distal to the stent segment (Figure-12).

### 2.4. Statistical Analysis

Continuous variables were reported as mean ± SD. Dichotomous variables were reported as percentage with 95 percent confidence interval, comparisons were formed with a Pearson chi-square test. For comparison of continuous data, a 2-tailed Student test or a non-parametric Mann Whitney-U test was performed when appropriate. A value of $P < 0.05$ was considered significant.
Figure-12. Vessel segment (VS) was defined as the segment bounded by side branches proximal (A) and distal (A’) to the stent segment. Target lesion (TL) encompassed the stent segment and edge segment. The length of the vessel covered by stent struts defined the stent segment (from B to B’). The edge segments encompassed the vessel 5 mm proximal (C) and distal (C’) to the stent.

2.5. Study endpoints:

The primary endpoint was the percentage stenosis at angiographic follow-up, as determined by quantitative angiographic analysis. The secondary angiographic endpoints included late loss, the rate of restenosis (defined as stenosis of more than 50% of the luminal diameter), and the in-stent minimal luminal diameter (MLD).

The secondary clinical endpoints included the incidence of death, the need for coronary bypass or intervention to treat clinical ischemia due to restenosis of the target lesion, and myocardial infarction (Q-wave or non-Q-wave) due to restenosis of the target lesion. Q-wave myocardial infarction was defined by the post-procedural of new Q waves greater than 0.04 second in two contiguous leads with an increase of creatine kinase level greater than twice the upper limit of normal and a creatine kinase MB fraction greater than twice the upper limit of normal.
Non-Q-wave myocardial infarction was documented on the basis of cardiac enzyme elevation (Troponin I > 0.1 ng/ml).

**Target lesion revascularization (TLR)** was defined as need of angioplasty or bypass surgery to treat angiographic diameter stenosis more than 50% within 5 mm proximal or 5 mm distal to the stent edges.

**Target vessel revascularization (TVR)** was defined as need to treat the lesions beyond stent segment.

**Target vessel failure (TVF)** was defined as TVR, MI, or cardiac death not attributed to a non-target vessel.

### 3- Results:

#### 3.1. Demographic and Clinical characteristics:

Between August 2002 and February 2004, 106 patients were enrolled: 54 in the Cypher group and 52 in the Paclitaxel group. Analysis of demographic and clinical characteristics are shown in table-7. Figure-13 represent risk factors in both groups.

#### 3.2. Angiographic results:

Forty patients (74%) in the Cypher group had de novo lesion versus 30 patients (57.7%) in the Paclitaxel group. The number of restenotic lesions was (Cypher, n=14 vs. Paclitaxel, n=22). Restenotic lesions were treated in 14 patients (Cypher) and 22 patients (Paclitaxel).

Coronary anatomy and lesion characteristics are given in table-8.
Table-7. Demographic and clinical characteristics of study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cypher group (n=54)</th>
<th>Paclitaxel group (n=52)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – y</td>
<td>61±10</td>
<td>59±11</td>
<td>0.32</td>
</tr>
<tr>
<td>Male – no (%)</td>
<td>41 (76)</td>
<td>37 (71.2)</td>
<td>0.47</td>
</tr>
<tr>
<td>Female – no (%)</td>
<td>13 (24)</td>
<td>15 (28.8)</td>
<td>0.55</td>
</tr>
<tr>
<td>Smoking – no (%)</td>
<td>26 (48.2)</td>
<td>15 (28.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes – no (%)</td>
<td>17 (31.5)</td>
<td>12 (23)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypertension – no (%)</td>
<td>45 (83.3)</td>
<td>52 (100)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypercholesterolemia – no (%)</td>
<td>52 (96.2)</td>
<td>50 (96.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>Obesity – no (%)</td>
<td>18 (33.3)</td>
<td>19 (36.5)</td>
<td>0.72</td>
</tr>
<tr>
<td>Family History – no (%)</td>
<td>13 (24)</td>
<td>16 (30.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Stable Angina – no (%)</td>
<td>48 (88.8)</td>
<td>39 (75)</td>
<td>0.14</td>
</tr>
<tr>
<td>Unstable Angina – no (%)</td>
<td>5 (9.2)</td>
<td>11 (21.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>NSTEMI – no (%)</td>
<td>1 (1.8)</td>
<td>2 (3.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>Prior MI – no (%)</td>
<td>10 (18.5)</td>
<td>10 (19.2)</td>
<td>0.78</td>
</tr>
<tr>
<td>Prior CABG – no (%)</td>
<td>11 (20.4)</td>
<td>7 (13.4)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

MI: Myocardial infarction, CABG: Coronary artery bypass graft. NSTEMI: Non-ST-Segment elevation myocardial infarction. Plus-minus values are mean±SD, frequency (%). P-value < 0.05 considered significant.
Figure-13. Risk factors in the both groups.

Before the procedure, lesion length was 12.82 ± 2.61 mm (Cypher) vs. 14.61 ± 2.83 mm (Paclitaxel) (P=0.15) and reference diameter (RD) was 3.02 ± 0.49 mm (Cypher) vs. 3.20 ± 0.26 mm (Paclitaxel) (P=0.20).

Before the procedure, there was no statistical difference of MLD between the two groups (Cypher, 0.90 ± 0.45 mm vs. Paclitaxel, 0.87 ± 0.42 mm; P=0.73).

After the procedure, MLD was also similar between the two groups (Cypher, 2.73 ± 0.47 mm vs. Paclitaxel, 2.80 ± 0.33 mm; P=0.32). Minimal luminal diameter at follow-up was (Cypher, 2.27 ± 0.62 mm vs. Paclitaxel, 2.34 ± 0.72 mm; P=0.57)

The diameter stenosis (DS%) at follow-up was (Cypher, 25.11 ± 18.24 vs. Paclitaxel 25.90 ± 21.23; P=0.83).
### Table-8. Characteristics of lesions in the both groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cypher group (n=54)</th>
<th>Paclitaxel group (n=52)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of diseased vessel – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (14.8)</td>
<td>16 (30.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>2</td>
<td>31 (57.4)</td>
<td>17 (32.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>3</td>
<td>15 (27.7)</td>
<td>19 (36.5)</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Target lesion – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>22 (40.7)</td>
<td>24 (44.4)</td>
<td>0.62</td>
</tr>
<tr>
<td>LCX</td>
<td>25 (46.3)</td>
<td>15 (28.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>RCA</td>
<td>6 (11.1)</td>
<td>11 (21.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>SVG</td>
<td>1 (1.8)</td>
<td>2 (3.8)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Type of lesion – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De novo</td>
<td>40 (74)</td>
<td>30 (57.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>ISR</td>
<td>14 (26)</td>
<td>22 (42.3)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Lesion classification – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>5 (9.2)</td>
<td>6 (11.5)</td>
<td>0.62</td>
</tr>
<tr>
<td>B1</td>
<td>20 (37)</td>
<td>17 (32.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>B2</td>
<td>19 (35.2)</td>
<td>15 (28.8)</td>
<td>0.38</td>
</tr>
<tr>
<td>C</td>
<td>10 (18.5)</td>
<td>14 (26.9)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

LAD: Left anterior descending, LCX: Left circumflex, RCA: Right coronary artery, SVG: Saphenous vein graft, ISR: In-stent restenosis, F/U: Follow-up. Plus minus values are mean ± SD, frequency %. P < 0.05 considered significant.
Angiographic analysis showed no significant differences of DS% before and after the procedure between two groups (70.25 ± 13.39 vs. 71.46 ± 14.27; P=0.65; 9.51 ± 9.42 vs. 10.40 ± 6.27; P=0.57; Cypher vs. Paclitaxel).

The rate of restenosis, defined as stenosis of more than 50%, was 12.9% in Cypher group in compare with 15.3% in Paclitaxel group (P=0.65). Table-9 summarizes the angiographic measurements.

Stent segment analysis revealed same late loss in both treatment groups (0.41± 0.58 mm vs. 0.45 ± 0.60 mm; P=0.71; Cypher vs. Paclitaxel). In addition, there was no significant difference of acute gain between two groups (1.79 ± 0.46 mm vs. 1.94 ± 0.47 mm; P=0.10; Cypher vs. Paclitaxel). Finally, the difference of loss index between the two groups was not statistically significant (Cypher, 0.34 ± 0.38 vs. Paclitaxel, 0.29 ± 0.42; P=0.59) (Table-9). See also figures-14, 15, 16, and 17.

3.3. Clinical events at follow-up:

The Major adverse cardiac events (MACE) are summarized in Table-10.

No patients in the both groups suffered from MI (either Q-wave or non Q-wave) at follow-up. The incidence of the death was 0% in the both groups.

In the Cypher group, 6 patients (11.1%) underwent percutaneous coronary interventions (PCIs) (either brachytherapy or drug-eluting stent implantation) at follow-up because of high-degree in-stent restenosis (ISR) within 5 mm proximal and 5 mm distal to the stent edges (TLR), and 1 patient (1.8%) underwent drug-eluting stent implantation due to high-degree restenosis beyond the stent segment (TVR).
Table 9. Angiographic measurements.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cypher group (n=54)</th>
<th>Paclitaxel group (n=52)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length (mm)</td>
<td>12.82 ± 2.61</td>
<td>14.61 ± 2.83</td>
<td>0.15</td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>3.02 ± 0.49</td>
<td>3.20 ± 0.26</td>
<td>0.20</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>70.25 ± 13.39</td>
<td>71.46 ± 14.27</td>
<td>0.65</td>
</tr>
<tr>
<td>After</td>
<td>9.51 ± 9.42</td>
<td>10.40 ± 6.27</td>
<td>0.57</td>
</tr>
<tr>
<td>At F/U</td>
<td>25.11 ± 18.24</td>
<td>25.90 ± 21.23</td>
<td>0.83</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.90 ± 0.45</td>
<td>0.87 ± 0.42</td>
<td>0.73</td>
</tr>
<tr>
<td>After</td>
<td>2.73 ± 0.47</td>
<td>2.80 ± 0.33</td>
<td>0.32</td>
</tr>
<tr>
<td>At F/U</td>
<td>2.27 ± 0.62</td>
<td>2.34 ± 0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td>0.41 ± 0.58</td>
<td>0.45 ± 0.60</td>
<td>0.71</td>
</tr>
<tr>
<td>Acute gain (mm)</td>
<td>1.79 ± 0.46</td>
<td>1.94 ± 0.47</td>
<td>0.10</td>
</tr>
<tr>
<td>Net gain (mm)</td>
<td>1.37 ± 0.57</td>
<td>1.64 ± 0.84</td>
<td>0.52</td>
</tr>
<tr>
<td>Loss index</td>
<td>0.34 ± 0.38</td>
<td>0.29 ± 0.42</td>
<td>0.59</td>
</tr>
<tr>
<td>Binary restenosis-no (%)</td>
<td>7 (12.9)</td>
<td>8 (15.3)</td>
<td>0.65</td>
</tr>
<tr>
<td>De novo lesions</td>
<td>3 (7.5)</td>
<td>3 (10)</td>
<td>0.06</td>
</tr>
<tr>
<td>In-stent restenosis</td>
<td>4 (28.5)</td>
<td>5 (22.7)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

MLD: Minimal luminal diameter, F/U: Follow-up.  
Plus-minus values are means ± SD. P < 0.05 considered significant.
Figure-14. Minimal luminal diameter (MLD) at follow-up.

Figure-15. Diameter stenosis (DS%) at follow-up.
Figure-16. Late loss at follow-up.

Figure-17. Acute gain at follow-up.
In the Paclitaxel group, 6 patients (11.5%) underwent PCIs for high-degree restenosis in lesion segment (TLR), and 2 patients (3.8%) were treated either with brachytherapy or drug-eluting stent implantation due to high-degree restenosis beyond the stent edges (TVR). Coronary artery bypass graft was not performed to any patient in the both groups at follow-up.

Two patients (3.7%) in the Cypher group had target vessel failure (TVF). The first patient had received a stent of a de novo lesion in segment 12 (Cypher stent was implanted in segments 11, 13) at 6-months follow-up, whereas the second one had undergone stent implantation of a de novo lesion in segment 7 distal to previously implanted Cypher stent at 6-month follow-up. In the Paclitaxel group, three patients (5.7%) had TVF. The first patient was treated with brachytherapy of in-stent restenosis (ISR) in segment 7 distal to the Paclitaxel stent. The second one was also treated with brachytherapy due to appearance of ISR in segment 6 proximal to the Paclitaxel stent, and the third one underwent PTCA of ISR in segment 8 distal to the Paxlitaxel stent (Table-10).

3.4. Subgroup analysis:

We divided the lesions into de novo lesions and in-stent restenosis lesions in order to compare the results of the two stents.

3.4.1. De Novo lesions (Cypher vs. Paclitaxel):

Seventy-four percent of patients who received Cypher stent had de novo lesions compared with 57.6% of patients who received Paclitaxel stent.

Before the procedure, DS% in the first group (69.75 ± 13.67%) and DS% in the second group (71.3 ± 15.96%) were similar (P=0.66). After the procedure, there was no significant difference of DS% between both groups (9.27 ± 9.27% vs. 10.5 ± 5.78%);
Finally, we did not find any significant difference of DS% between the two groups at follow-up (Cypher, $21.12 \pm 16.44\%$ vs. Paclitaxel, $22.8 \pm 19.78\%; P=0.73$) (Figure-18).

Pre-procedural minimal luminal diameter (MLD) was similar in the both groups ($0.91 \pm 0.44$ mm vs. $0.88 \pm 0.49$ mm; $P=0.85$; Cypher vs. Paclitaxel). Also, there was no significant difference of post-procedural MLD ($2.70 \pm 0.43$ mm vs. $2.79 \pm 0.43$ mm; $P=0.33$; Cypher vs. Paclitaxel).

**Table-10. Clinical events at follow-up.**

<table>
<thead>
<tr>
<th>Events</th>
<th>Cypher (n=54)</th>
<th>Paclitaxel (n=52)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death – no (%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>MI – no (%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Q-wave</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Non Q-wave</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>TLR – no (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TL-CABG</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>TL-PCI</td>
<td>6 (11.1)</td>
<td>6 (11.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>TVR – no (%)</td>
<td>1 (1.8)</td>
<td>2 (3.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>TVF – no (%)</td>
<td>2 (3.7)</td>
<td>3 (5.7)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

MI: Myocardial infarction, TLR: Target lesion revascularization, TVR: Target vessel revascularization, CABG: Coronary artery bypass graft, TVF: Target vessel failure, PCI: Percutaneous coronary intervention.
Figure-18. Diameter stenosis (DS%) of de novo lesions at follow-up.

Minimal luminal diameter of Cypher group at follow-up was the same as MLD of Paclitaxel group at follow-up (2.35 ± 0.56 mm vs. 2.40 ± 0.69 mm; P=0.73, respectively) (Figures-19, 20, 21).

Angiographic analysis showed no differences of late loss, acute gain, loss index, as well as net gain among the patients of both groups. Binary restenosis (BR), defined as stenosis diameter more than 50%, was detected in 3 patients (7.5%) in the Cypher group compared with 3 patients (10%) in the Paclitaxel group (P=0.07).

Table-11 summarized the angiographic results of de novo lesions. Clinical events including TLR, TVR, TVF, death, and MI are summarized in Table-12.
3.4.2. Restenotic lesions (Cypher vs. Paclitaxel):

Fourteen patients (25.9%) in the Cypher group compared with 22 patients (42.3%) in the Paclitaxel stent had in-stent restenosis lesions. Before procedure, minimal luminal diameter (MLD) was similar between the two groups (0.87 ± 0.49 mm vs. 0.84 ± 0.32 mm; P=0.84; Cypher vs. Paclitaxel). In addition, diameter stenosis (DS%) in the Cypher group (71.71± 12.95%) was the same as DS% of Paclitaxel group (71.60 ± 11.96%) (P=0.99). There was no significant difference of post-procedural DS% between the two groups (10.21 ± 10.16% vs. 10.27 ± 7.02%; P=0.98; Cypher vs. Paclitaxel). Post-procedural MLD in the Cypher group was (2.80 ± 0.58 mm), and (2.82 ± 0.30 mm) in the Paclitaxel group (P=0.92) (Figures-22, 23).

Angiographic analysis at follow-up showed no significant difference of MLD and DS% between the two groups (2.03 ± 0.75 mm vs. 2.11± 0.79 mm; 36.50 ± 18.91% vs. 32.45 ± 24%; Cypher vs. Paclitaxel, respectively) (Figures-24, 25).
Figure-20. Minimal luminal diameter of de novo lesions (n=40) in the Cypher group. 1= MLD before, 2= MLD after, 3= MLD at follow-up.

Figure-21. Minimal luminal diameter of de novo lesions (n=30) in the Paclitaxel group. 1= MLD before, 2= MLD after, 3= MLD at follow-up.
Table-11. Angiographic measurements of de novo lesions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cypher (n=40)</th>
<th>Paclitaxel (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter stenosis %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>69.75 ± 13.67</td>
<td>71.30 ± 15.96</td>
<td>0.66</td>
</tr>
<tr>
<td>After</td>
<td>9.27 ± 9.27</td>
<td>10.50 ± 5.78</td>
<td>0.52</td>
</tr>
<tr>
<td>Follow-up</td>
<td>21.12 ± 16.44</td>
<td>22.6 ± 19.76</td>
<td>0.73</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.91 ± 0.44</td>
<td>0.88 ± 0.49</td>
<td>0.85</td>
</tr>
<tr>
<td>After</td>
<td>2.70 ± 0.43</td>
<td>2.79 ± 0.34</td>
<td>0.33</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2.35 ± 0.56</td>
<td>2.40 ± 0.69</td>
<td>0.73</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td>0.33 ± 0.49</td>
<td>0.36 ± 0.51</td>
<td>0.78</td>
</tr>
<tr>
<td>Acute gain (mm)</td>
<td>1.79 ± 0.45</td>
<td>1.92 ± 0.52</td>
<td>0.24</td>
</tr>
<tr>
<td>Net gain (mm)</td>
<td>1.44 ± 0.55</td>
<td>1.52 ± 0.91</td>
<td>0.65</td>
</tr>
<tr>
<td>Loss index</td>
<td>0.25 ± 0.22</td>
<td>0.28 ± 0.50</td>
<td>0.71</td>
</tr>
<tr>
<td>BR – no (%)</td>
<td>3 (7.5)</td>
<td>3 (10)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

MLD: Minimal luminal diameter, BR: Binary restenosis.
Table 12. Clinical events at follow-up of patients with de novo lesions.

<table>
<thead>
<tr>
<th>Events</th>
<th>Cypher (n=40)</th>
<th>Paclitaxel (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death – no (%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>MI – no (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q-wave</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Non Q-wave</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>TLR – no (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TL-CABG</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>TL-PCI</td>
<td>2 (5)</td>
<td>2 (6.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>TVR – no (%)</td>
<td>0</td>
<td>1 (3.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>TVF – no (%)</td>
<td>2 (5)</td>
<td>2 (6.6)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

MI: Myocardial infarction, TLR: Target lesion revascularization, TVR: Target vessel revascularization, CABG: Coronary artery bypass graft, TVF: Target vessel failure, PCI: Percutaneous coronary intervention. P < 0.05 considered significant.
Figure-22. Diameter stenosis (DS%) of restenotic lesions at follow-up.

Figure-23. Minimal luminal diameter of restenotic lesions at follow-up.
On the other hand, there were no significant differences of the other angiographic parameters (Late loss, acute gain, net gain, and Loss index). Table-13 shows the angiographic parameters of restenotic lesions in the both groups.

Table-13. Angiographic parameters of restenotic lesions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cypher (n=14)</th>
<th>Paclitaxel (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter stenosis %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>71.71± 12.95</td>
<td>71.68 ± 11.96</td>
<td>0.99</td>
</tr>
<tr>
<td>After</td>
<td>10.21± 10.16</td>
<td>10.27 ± 7.02</td>
<td>0.98</td>
</tr>
<tr>
<td>Follow-up</td>
<td>36.5 ± 18.91</td>
<td>32.45 ± 24</td>
<td>0.59</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0.67 ± 0.49</td>
<td>0.84 ± 0.32</td>
<td>0.84</td>
</tr>
<tr>
<td>After</td>
<td>2.80 ± 0.58</td>
<td>2.82 ± 0.30</td>
<td>0.84</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2.03 ± 0.75</td>
<td>2.11 ± 0.79</td>
<td>0.92</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td>0.76 ± 0.48</td>
<td>0.70 ± 0.69</td>
<td>0.78</td>
</tr>
<tr>
<td>Acute gain (mm)</td>
<td>1.93 ± 0.39</td>
<td>1.97 ± 0.41</td>
<td>0.76</td>
</tr>
<tr>
<td>Net gain (mm)</td>
<td>1.17± 0.59</td>
<td>1.26 ± 0.68</td>
<td>0.74</td>
</tr>
<tr>
<td>Loss index</td>
<td>0.41± 0.30</td>
<td>0.39 ± 0.36</td>
<td>0.88</td>
</tr>
<tr>
<td>BR – no (%)</td>
<td>4 (28.5)</td>
<td>5 (22.7)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

MLD: Minimal luminal diameter, BR: Binary restenosis.
Clinical events at follow-up including TLR, TVR, death, and MI were similar between the two groups. However, there was no difference in TVF between the two groups (P=0.05). Table-14 summarized the clinical events of restenotic lesions in the two groups.

Table-14. Clinical events at follow-up of restenotic lesions.

<table>
<thead>
<tr>
<th>Events</th>
<th>Cypher (n=14)</th>
<th>Pxlitaxel (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death – no (%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>MI – no (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q-wave</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Non Q-wave</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>TLR – no (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TL-CABG</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>TL-PCI</td>
<td>4 (28.5)</td>
<td>4 (18.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>TVR – no (%)</td>
<td>1 (7.14)</td>
<td>1 (4.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>TVF – no (%)</td>
<td>0</td>
<td>1 (4.5)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

MI: Myocardial infarction, TLR: Target lesion revascularization, TVR: Target vessel revascularization, CABG: Coronary artery bypass graft, TVF: Target vessel failure, PCI: Percutaneous coronary intervention. P < 0.05 considered significant.

Figures-26, 27 represent two examples of patients who received either Sirolimus-eluting stent or Paclitaxel-eluting stent, these figures show no in-stent restenosis at 6-month follow-up.
Figure-24. Minimal luminal diameter of restenotic lesions (n=14) in the Cypher group. 1= MLD before, 2= MLD after, 3= MLD at follow-up.

Figure-25. Minimal luminal diameter of restenotic lesions (n=22) in the Paclitaxel group. 1= MLD before, 2= MLD after, 3= MLD at follow-up.
Figure-26. Example of patient who received sirolimus-eluting stent in proximal segment 6 of left anterior descending artery. A: before stenting, B: after, and C: at 6-month follow-up.
Figure-27. Example of patient who received paclitaxel-eluting stent in proximal segment 7 of left anterior descending artery. A: before stenting, B: after, and C: at 6-month follow-up.
4-Discussion:

We investigated the in-stent restenosis (ISR) rate of sirolimus-eluting and paclitaxel-eluting stents. The main finding of our study is that the sirolimus-eluting and paclitaxel-eluting stents appear equally effective and safe in reducing the restenosis rate (12.9% vs. 15.3%). In addition, comparison of de novo and restenotic lesions between the 2 stents showed no significant difference of restenosis rates at follow-up (de novo, 7.5% vs. 10%; restenosis, 28.5% vs. 22.7%; Cypher vs. Paclitaxel).

No deaths or MI were reported at follow-up. Target lesion revascularization, target vessel revascularization, and target vessel failure rates were similar between the two groups.

The Cypher stent has a much better data basis, we know much more about it than about the Cook stent. Accordingly, it is important to establish that the Cook stent is not apparently inferior to the Cypher stent. Therefore, our observational study tested the efficacy and safety of the **Cook stents** (paclitaxel-eluting without a polymer) in comparison with the **Cypher stents** (sirolimus-eluting). The sirolimus-eluting stents used in this study were composed of a tubular stainless steel stent, the **Bx Velocity** stent (Cordis), coated with a 5-µg-thick layer of nonerodable polymer blended with sirolimus. The paclitaxel-eluting stents were **V-Flex** stents (Cook) impegrated directly with paclitaxel without a polymer. In contrast, The Milan DES experience compared **Cypher stents** with **Taxus stents** (polymer-based paclitaxel-eluting stent) which was presented at the American Heart Association (AHA) scientific sessions 2004 [9]. In this trial 1362 patients underwent Drug-Eluting Stent (DES) implantation – 921 received the Cypher stents and 441 patients received the Taxus stents. At 30 days, revascularization of target lesion was performed in one patient in the Cypher group versus 2 patients in
the Taxus group. Three patients in each group developed subacute thromboses (P=0.3). The overall MACE were similar between the both groups (Cypher, 3 patients vs. Taxus, 3 patients). In the Cypher group 457 patients underwent clinical follow-up at 6 months. TLR was performed in 71 patients (15.5%), while 83 patients (18%) underwent TVR. Further, this trial compared efficacy and safety between the Cypher and Taxus stents in chronic total occlusion (CTO). Sixty-nine patients received Taxus stents, while 132 patients received Cypher stents. In the Taxus arm angiographic follow-up was available in 10 (15%) of patients. MLD at follow-up was 2.92 ± 0.61 mm, and DS% was 11± 10%. Clinical follow-up was performed at 5 ± 2.9 months. Three patients (4.3%) had TLR, and 3 patients (4.3%) had TVR. MACE were reported in 3 patients (4.3%). In Cypher arm angiographic follow-up was available in 49% of patients. MLD at follow-up was 1.66 ±1.02 mm, and DS% was 45 ± 32%. Clinical follow-up was done at 9 ± 4.4 months. Fifteen patients (11.3%) had TRL, and 18 patients (18%) had TVR. MACE were reported in 19 patients (14.4%). So what does this mean – there was no statistical difference in outcome in this preliminary, small experience.

Moreover, Omar AR et al. [36] compared the Cypher and Taxus (polymer-based paclitaxel-eluting) stents in PCI of complex coronary stenoses. This trial was conducted at National University Hospital, Singapore, which was presented at scientific sessions of the American Heart Association 2003. Dr Omar reviewed outcomes of 145 patients – 58 received Cypher stents and 87 received Taxus stents. Ninety-six percent of the target lesions were de novo, while 4% had undergone previous PCI. At 30 days, revascularization of the target vessel was required in 2 patients – one in each arm – and one Taxus patient developed subacute stent thrombosis a week after the procedure. There was a trend at 30 days toward lower MACE rates in the Taxus arm than in the Cypher arm (8% vs. 15.5%), but this was not sustained at 6 months, when the rate in
the Taxus arm was 2.4% vs. 1.9% in the Cypher arm. Moreover, there was a statistically significant larger mean reference diameter (2.83 vs. 2.68 mm) and post-minimal luminal diameter (2.87 vs. 2.66 mm) in the Taxus arm (P<0.001). At 6 months, there was significant difference in clinical outcomes even though the patients in the Cypher arm had more complex lesions.

Over the past decade, the use of stents has become common practice during percutaneous coronary intervention (PCI), especially after clinical trials showed evidence of decreased restenosis rates when compared with balloon angioplasty alone [6, 50]. Although stents significantly reduce restenosis when compared with balloon angioplasty, restenosis rates in patients who receive stents are still 20% to 40% at 6 months [1]. Recently, noval local drug delivery systems using coated stent technologies that elute potent antiproliferative agents resulted in another dramatic reduction in restenosis rates, with rates now less than 10% in short-term follow-up. This success has resulted from largely empiric selection of drugs, using anti-neoplastic and immunosuppressant agents [49]. Drug-eluting stents offer theoretical advantages over systemic pharmacologic therapy, such as higher drug concentrations at the site of stent deployment and minimal systemic side effects. Among drug-eluting stents, sirolimus and paclitaxel-eluting stents showed promise in reducing in-stent restenosis as explained above [1].

Our study showed no difference of diameter stenosis (DS%) at follow-up between the two groups (25.11±18.24% in the Cypher group vs. 25.90 ± 21.23% in the Paclitaxel group; P=0.83). Binary restenosis (BR), defined as stenosis > 50%, was detected in 7 patients (12.9%) in the Cypher group versus 8 patients (15.3%) in the Paclitaxel
Minimal lumen diameter (MLD) at follow-up was similar between the two groups (Cypher, 2.27 ± 0.62 mm vs. Paclitaxel, 2.34 ± 0.72 mm; P=0.57). In addition, no significant difference of late loss was detected (Cypher, 0.41 ± 0.58 mm vs. Paclitaxel, 0.45 ± 0.60 mm; P=0.71). Other angiographic parameters (acute gain, loss index, and net gain) were the same in the both groups.

No patients in either group suffered from myocardial infarction during the follow-up duration or died due to cardiac cause. In addition, no one underwent bypass surgery (CABG) for revascularization of the target lesion. Six patients (11.1%) in the Cypher group treated either with brachytherapy or with drug-eluting stents due to high-degree in-stent restenosis within 5 mm proximal and 5 mm distal to the stent edges (TLR) compared with 6 patients (11.5%) of the Paclitaxel group (P=0.78). Furthermore, the difference of TVR and TVF between the two groups was not statistically significant (P=0.44, 0.52 respectively).

We compared the effectiveness of both stents on de novo lesions and restenotic lesions. Diameter stenosis (DS%) at follow-up was the same either in de novo lesions subgroup (Cypher, 21.12 ±16.44% vs. Paclitaxel, 22.6 ±19.76%; P=0.73) or in restenotic lesions subgroup (Cypher, 36.5 ±18.91% vs. Paclitaxel, 32.45 ±24%; P=0.59). Furthermore, restenosis rate in de novo lesions was similar in the both groups (7.5% vs. 10%; P=0.06; Cypher vs. Paclitaxel) as it was in restenotic lesions (28.5% vs. 22.7%; P=0.07, respectively). Other angiographic parameters were the same between the Cypher and Paclitaxel stents in the both subgroups. Overall, there was no difference in the incidence of target lesion revascularization (TLR) for both de novo lesions and restenotic lesions (de novo lesions, 5% vs. 6.6%; P=0.06, restenotic lesions, 28.5% vs. 18.2%; P=0.08, Cypher vs. Paclitaxel respectively). One patient (3.3%) who received a paclitaxel-eluting stent for the treatment of de novo lesions underwent PCI in order to treat high-degree
stenosis beyond the stent margins (TVR) whereas no one in the Cypher group had TVR (P=0.04). In addition, TVF was the same between Cypher and Paclitaxel stents in de novo subgroup (5% vs. 6.6%; Cypher vs. Paclitaxel respectively; P=0.06). one patient (4.5%) who received a paclitaxel-eluting stent for the treatment of in-stent restenosis (ISR) was treated with brachytherapy proximal to previously implanted drug-eluting stent (TVF) whereas no one in the Cypher group had TVF (P=0.05). Moreover, TVR was the same between Cypher and Paclitaxel stents in restenotic lesion subgroup (7.14% vs. 4.5% respectively; P=0.09). From these results we can conclude that the Paclitaxel-eluting stents are equally effective and safe as the Sirolimus-eluting stents.

Some limitations of our study should be noted. First, sample size was small. This is explained by the relatively infrequent use of the novel stents and the necessity to obtain a follow-up examination. However, such a comparison has – to our best knowledge – not been performed elsewhere in Germany, and it should help to increase our knowledge regarding the clinical outcome of these stents. Second, our study was observational, and patients were not randomized. It is possible that confounding factors played a role which were not accounted. Also, there were some demographic differences, which appeared, however, to be very minor. Finally, with limitations in the duration of follow-up and sample size, it is possible that differences between the groups were present but were not detected. We consider this unlikely, because neither in the angiographic parameters nor in the clinical data, trend in favor for one or the other stent system was observed.

**Conclusions:** In this clinical observational study, we did not observe significant differences between the sirolimus-coated Cypher stent and the non-polymer paclitaxel-coated Cook stent in terms of angiographic follow-up parameters and binary restenosis
rate. Because our study was too small and not randomized, it does not allow statements on differences in short-term or long-term performance of the stent systems. However, the lack of substantial differences in 6-month outcome compared with the well-established sirolimus-coated Cypher stent suggest that the non-polymer paclitaxel-coated Cook stent is reasonably safe and effective.
5- Summary:

The aim of the current study was to compare the restenosis rate between sirolimus-eluting and paclitaxel-eluting stents. One hundred six patients were included who received either the sirolimus-eluting stents (n=54) or the paclitaxel-eluting stents (n=52) for the treatment of de novo lesions or in-stent restenosis (ISR).

Primary endpoint was diameter stenosis (DS%) at follow-up. Angiographic secondary endpoints included late loss, rate of restenosis (defined as stenosis > 50% of luminal diameter), and the in-stent minimal luminal diameter (MLD) at follow-up. Clinical secondary endpoints were death rate, MI (Q-wave and non-Q wave, CABG, TLR, TVR and TVF at follow-up.

Diameter stenosis (DS%) at follow-up was similar between the two groups (25.11±18.24% vs. 25.90 ± 21.23%;P=0.83, respectively). Minimal luminal diameter (MLD) at follow-up was also similar between the two groups (Cypher, 2.27 ± 0.62 mm vs. Paclitaxel, 2.34 ± 0.72 mm; P=0.57). Seven patients in the Cypher group and eight patients in the Paclitaxel group had binary restenosis (12.9% vs. 15.3%; P=0.65, respectively). Other angiographic parameters including late loss, acute gain, loss index, and net gain were similar between the two groups. Regarding clinical events, no one in either group suffered from MI or died or underwent bypass surgery. Also we did not find significant differences of TLR, TVR, and TVF between the two groups.

In conclusion, Although some limitations apply, in particular the retrospective nature of our study and the small cohort size, our results suggest that compared with the well established rapamycin-eluting stent, the paclitaxel-eluting stent without polymer-coating performs reasonably well.
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7- Abbreviations:

AHA: American Heart Association.
ACC: American College of Cardiology.
CABG: Coronary Artery Bypass Graft.
CAD: Coronary Artery Disease.
DCA: Directional Coronary Atherectomy.
DS: Diameter Stenosis.
EC: Endothelial Cell.
EEL: External Elastic Lamina.
I-B: Inhibitory Protein-B
ICAM-1: Intercellular Adhesion Molecule-1.
IEL: Internal Elastic Lamina.
IL: Interleukin.
ISR: In-Stent Restenosis.
IVUS: Intravascular Ultrasound.
MACE: Major Adverse Cardiac Events.
MCP-1: Monocyte Chemoattractant Protein-1.
MI: Myocardial Infarction.
MLD: Minimal Luminal Diameter.
NF-B: Nuclear Factor-B.
PCI: Percutaneous Coronary Intervention.
PTCA: Percutaneous Transluminal Coronary Angioplasty.
QCA: Quantitative Coronary Angiography.
ROS: Reactive Oxygen Spices.
SVG: Saphaneous Vein Graft.
TLR: Target Lesion Revascularization.
TNF: Tumor Necrosis Factor.
TVF: Target Vessel Failure.
TVR: Target Vessel Revascularization.
VCAM-1: Vascular Cell Adhesion Molecule-1.
VSMC: Vascular Smooth Muscle Cell.
8- Acknowledgment:

It is my pleasure to express deep gratitude to the person who invited me to his country and gave me the chance to do this research project presenting all the expected and the non-expected facilities to lead this work to perfection. My thanks to Prof. Dr. med. R. Erbel. Words can never thank OA. PD. Dr. med. A. Schmermund for his sincere guidance, efforts, support and extreme patience throughout the conduct of this work. I thank my colleague Dr. med. C. Naber for his kind assistance in doing QCA analysis. It is also important to thank those individuals in the catheter laboratory who gave me so much of themselves so that the clinical procedures could run smoothly.
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