

## CLINICAL IMPACT OF DRUG-ELUTING CORONARY STENTS. REVIEW.

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Andreas Gruentzig ilk defa 1977 yılında pekütan balon anjiyoplastiyi başarıyla uygulamıştır.

PTCA'nın dezavantajı, lezyon lokalizasyonu, lezyon uzunluğu, diyabet mevcudiyeti, damar çapı ve diğer faktörlere bağlı olmak üzere %25-50 oranında restenoz olmasıdır. 1993 yılında tamamlanmış iki randomize çalışma, BENESTENT VE STRESS balon anjiyoplasti ile stent yerleştirilmesini kıyaslamıştır. Bu çalışmanın sonuçları, Palmatz-Schatz stent yerleştirilmesinden sonra restenoz oranında önemli azalma olduğunu göstermiştir. Stent yerleştirilmesinden sonra restenoz da önemli oranda azalma olmasına rağmen restenoz hala %25-30 oranında olmaktadır. Bazı otoriteler oral antiproliferatif ve immunosupressiv ilaç vermekle restenoz oranında azalma olacağı düşüncesi ile çıplak metal stent

yerleştirilmesinden sonra rapamycin'in oral yolla verilmesiyle elde edilen sistemik etkilerinin sonuçları restenoz oranında azalma yapmamıştır. İlaç salgılayan stentlerin daha etkin ve güvenli olabileceği seçeneğinin daha doğru olduğu düşünülmüştür. İlaç salınımlı stentler klinik pratikte başarıyla kullanılarak çıplak metal stentlerle MACE olaylarının aynı oranda olduğu gösterilirken, neointimal proliferasyonu ve restenoz oranını önemli oranda azaltmıştır.

Sonuç Yeni tip ilaç salınımlı stentlerin yapılması rekabeti artıracak ve fiyatlarda azalmaya neden olacaktır.

**Anahtar kelimeler:**İlaç kaplı stent, Restenoz

(Türk Girişimsel Kard. Der. 2006;10:166-172)

### GİRİŞ

Percutaneous transluminal coronary angioplasty (PTCA) was first successfully performed by Andreas Gruentzig in 1977 [1]. Significant advantages of coronary angioplasty made it a widely spread and universally recognized technique. As early as 1990s PTCA became the most common type of coronary revascularization procedure. In 2000 alone more than 550 000 PTCA procedures were performed in the United States [2]. However, the disadvantage of PTCA is high restenosis rate, which can range from 25 to 50% depending on the vessel diameter, lesion location and length, presence of diabetes mellitus and other factors [3,4]. Restenosis after balloon angioplasty is caused by elastic recoil, negative remodeling and neointimal proliferation.

With the advent of intracoronary stenting into interventional cardiology clinical practice in late

1980s, there has been a considerable decrease in procedural complication rates due to the stent design that efficiently prevents elastic recoil and negative remodeling of a vessel.

In 1993 two completed randomized trials demonstrated advantages of stenting compared with balloon angioplasty. BENESTENT and STRESS trials documented significant reduction in restenosis rates after Palmaz-Schatz stent placement [5,6]. However, although much lower restenosis rates have been demonstrated after stenting compared to PTCA, they are still considerable and range from 20 to 30% [6,7]. Moreover, different factors cause restenosis after stent placement compared to PTCA. The mechanism of in-stent-restenosis (ISR) relates to cascade reactions in response to the damage of endothelial layer and vessel wall inflammation resulting in neointimal proliferation and smooth muscle cell migration. Flow-limiting ISR is defined as an in-stent lumen loss of 50 % or more, which occurs most frequently at 3 to 6 months after stenting [8]. Therefore, methods are being developed to further

reduce if not eliminate restenosis.

Some authors believed that pharmacotherapy with oral antiproliferative and immunosuppressive agents could become an efficient and cheap way to prevent restenosis. In 2004 a small trial assessed the efficiency of oral sirolimus (rapamycin) in inhibiting in-stent neointimal hyperplasia [9]. The trial enrolled 15 patients, each treated with 1 bare metal stent placed into the native coronary artery stenosis. All the patients received aspirin, clopidogrel and atorvastatin for 6 months. The loading dose of rapamycin was 5 mg followed by 2 mg per day for 4 weeks. At 10 days since the beginning of the therapy the blood serum rapamycin level was  $7.9 \pm 2.6$  ng/ml (versus 5-15 ng/ml serum rapamycin after kidney transplantation). Angiography was performed at  $6.0 \pm 0.7$  months. Late lumen loss was  $1.4 \pm 1.1$  mm; restenosis developed in 6 out of 15 patients (40%). Thus, systemic administration of rapamycin did not reduce in-stent neointimal proliferation, and the rate of restenosis exceeded the mean frequency of restenosis after conventional stenting.

There have been other attempts to reduce restenosis using systemic pharmacological treatment, but they were also unsuccessful [10,11], in part because systemically administered agents failed to reach required concentration at the stent location.

Delivery of a therapeutic agent with stents proved to be a more justified approach. Using a stent platform for drug delivery can be called an ideal option, because it allows to deliver a therapeutic agent directly to the target site, reduce medication doses significantly and eliminate their systemic and side effects.

The difference between drug-eluting stents and bare-metal stents lies not only in the presence of a medication. An important component to a drug-eluting stent is a polymer, which acts as a therapeutic agent container and allows for its sustained release. The main requirements for the stent polymer coating are as follows: the polymer should be pharmacologically inert, resistant to mechanical pressure during the stent placement, retain its properties after sterilization, and ensure timed-release of the medication [12]. Besides, a polymer should not cause vessel wall inflammation or possess thrombogenic properties.

Stent design can also have an influence on restenosis. A.Kastrati et al found that the rates of restenosis and target vessel revascularization were significantly lower in patients treated with thin-strutted (50  $\mu$ m) stents versus those treated with thick-strutted (140  $\mu$ m) stents [13].

A number of agents that have been used efficiently by other branches of medicine are currently employed by interventional cardiology as eluting

substances/agents. However, only a few drug-eluting stents have been approved by Food and Drug Administration (FDA), which thoroughly evaluates the products' effectiveness and safety, and are used routinely. Other drug eluting systems require further investigation and testing on animal models.

### Sirolimus-Eluting Stents

The Cypher stent (Cordis, Johnson & Johnson) contains sirolimus (rapamycin) and is the first drug-eluting stent approved for clinical use. Sirolimus is a macrolide natural antibiotic first discovered as a product of the bacterium *Streptomyces hygroscopicus* and has potent anti-inflammatory and immunosuppressive properties [14]. Originally sirolimus was developed as an antifungal agent. However, in 1999 it received FDA's approval as a drug to prevent rejection of kidney transplants [15]. Besides, sirolimus is a strong inhibitor of smooth muscle cell proliferation and migration [16]. This effect is linked to the suppression of mTOR (mammalian Target of Rapamycin) kinase activity that ultimately blocks cell growth in phase G1 [17].

FIM (First-In-Man) was the first clinical trial of sirolimus-eluting intracoronary stents. It was conducted simultaneously in Sao Paulo (Brazil) and Rotterdam (the Netherlands) [18,19]. The trial comprised 32 patients with stable angina and 13 patients with unstable angina. In Sao Paulo the patients were treated with standard metal balloon-expandable BX Velocity stents (Cordis, Johnson & Johnson), 18 mm long, with different release formulations of rapamycin elution: slow-release formulation SES (?28 days), and fast-release formulation SES (< 15 days). In Rotterdam only slow-release SES were used. All the patients received dual antiplatelet therapy of clopidogrel (a 300 mg loading dose followed by 75 mg daily) for 60 days after the procedure, and aspirin 325 mg per day, indefinitely. Sao Paulo patients were examined again at 4 months after the procedure. In-stent lumen loss was only  $0.09 \pm 0.30$  mm in the slow-release group and  $-0.1 \pm 0.3$  mm in the fast-release group. The mean rate of neointimal hyperplasia in both groups was 10.7% compared to the rates of 19 to 48% in patients treated with bare metal stents [20,21]. The outcomes for Rotterdam patients treated with drug-eluting stents were evaluated at 6 months with similar results: in-stent lumen loss was 0 mm, neointimal hyperplasia rate -  $2.00 \pm 4.98\%$ . The advantage of the slow-release formulation SES over the fast-release formulation SES was preserved at 4-year follow-up: in-stent lumen loss was 0.1 mm and 0.3 mm, respectively.

RAVEL (Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent) was

the next trial evaluating SES. This double-blind, randomized, placebo-controlled trial enrolled 238 patients who were allocated between sirolimus-eluting Cypher stents and the prototype bare-metal BX Velocity stents [22]. Sirolimus-eluting stents had a slow-release formulation. All the patients included in the trial received heparin during the procedure and a dual antiplatelet therapy: clopidogrel or ticlopidine for 8 weeks after the procedure and aspirin 100-325 mg or more, indefinitely. The 6-months-results demonstrated a considerable advantage of the sirolimus-eluting stents over the bare metal stents. In-stent lumen loss was -0.01 mm for the SES group versus 0.80 mm ( $p < 0.001$ ) for the BMS group. At 1 year the results were the same. Sirolimus-eluting stents were particularly efficient for patients with diabetes mellitus (19 patients received SES, and 25 patients - BMS): the lumen loss was 0.07 mm vs 0.82 mm, respectively ( $p < 0.001$ ). Restenosis rate decreased from 41.7% in the BMS group to 0 in the SES group irrespective of the vessel diameter [23,24].

The randomized, double-blind SIRIUS (Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions) trial of 1058 patients from 53 US centers evaluated SES in patients with more complex coronary anatomy. This cohort included patients with the more complex disease and history than the RAVEL population: longer lesions (mean 14.4 mm vs 9.6 mm), diabetic patients (26% vs 19%), patients with multivessel disease (40.7% vs 29.2%). 60% of the patients received therapy with GP IIb/IIIa inhibitors (vs 10% in RAVEL) [25]. Coronary angiography at 8 months in 85% of the patients demonstrated a binary ISR rate of 35.4% in the bare metal group vs only 3.2% in the SES group ( $p < 0.001$ ), and a rate of edge restenosis of 36.3% in the bare metal group vs 8.9% in the SES group ( $p < 0.001$ ). Lumen loss was  $1.00 \pm 0.70$  mm and  $0.17 \pm 0.45$  mm, respectively ( $p < 0.001$ ) [26]. Thus, the rate of restenosis in the SIRIUS trial was higher than in the FIM trial, but at least two times lower than after bare metal stents implantation. Based on the SIRIUS trial findings the sirolimus-eluting Cypher (ex BX Velocity) stent received FDA approval for clinical use. The data accumulated in the European E-SIRIUS project [27] and Canadian ?-SIRIUS trial [28] have confirmed SIRIUS results for other patient subsets.

### Paclitaxel-Eluting Stents

Paclitaxel is a natural alkaloid with a unique mechanism of cytostatic action. The crude extract containing the component was obtained from the bark of the Pacific yew tree, *Taxus brevifolia*, which grows in the North-West of the US and Canada. In 1960-s preclinical data demonstrated high cytostatic activity of crude paclitaxel extract in a broad range of tumors.

In 1971 paclitaxel was isolated from the bark extract as an active agent [29,30]. In 1980-90s it was researched as a treatment for breast, lung and other cancers [31,32]. Currently it is used in oncology as a wide spectrum chemotherapy drug. Paclitaxel efficiently interferes with the normal function of microtubule growth. It inhibits mitogen-activated protein kinase - an enzyme that causes depolymerization of microtubules. Besides, paclitaxel can directly cause polymerization of microtubules. As a result, the cell cycle is arrested in M-phase [33]. Paclitaxel's unique properties ensure a long antiproliferative effect even after its one-time, low dose administration. This makes it an excellent agent for local medical therapy.

TAXUS-I was the first clinical study of the paclitaxel-eluting stent [34]. There were 61 patients randomly allocated between the 15 mm paclitaxel-covered TAXUS NIR stent system (Boston Scientific) and the bare metal NIR stent. A carbon-based polymer was used in the paclitaxel-NIR stent system, which allowed the biphasic release of paclitaxel: the first phase lasted for 48 hours since the stent placement, the second phase comprised slow medication release for the following 10 days. All the patients received a 300-mg loading dose of clopidogrel followed by 75 mg a day for 6 months, and aspirin 80 mg a day for 12 months. In the paclitaxel-eluting (PES) group in-stent lumen loss was reduced by 50%, and neointimal hyperplasia was reduced by 30% compared to the control group. At 9 months none of the patients developed restenosis in the PES group. At 12 months, the MACE rates were the same in both groups. Boston Scientific research program was continued in TAXUS-II, TAXUS-III and TAXUS-IV trials, and confirmed the advantage of PES over BMS [35,36,37].

TAXUS-V and TAXUS-VI trials included patients with a more complex coronary disease (long lesions, coronary arteries less than 2.5 mm in diameter) to evaluate paclitaxel-coated EXPRESS stents. North America TAXUS-V trial studied slow-release formulation stents in high-risk lesions [38]. TAXUS-VI trial studied medium-release formulation EXPRESS stents [39].

The ELUTES (European Evaluation of pacliTaxel-Eluting Stent) trial evaluated the safety and efficacy of paclitaxel-eluting stents with nonpolymer coating [40]. 192 patients were randomized to receiving paclitaxel-eluting V-Flex Plus PTX stents (Cook Inc.) of four different dosages: 0.2 mcg/mm; 0.7 mcg/mm; 1.4 mcg/mm and 2.7 mcg/mm, or an bare-metal V-Flex Plus stent. At 6 months the late lumen loss was lowest in the 2.7 mcg/mm group at 0.1 mm vs 0.73 mm in the control group ( $p = 0.002$ ), albeit the rate of MACE was the same for both groups at 11%. At 12 months the rate of revascularization was 5% in the high dose (2.7 mcg/mm) group vs 16% in the control

group. Based on the ELUTES study data V-Flex Plus PTX stent system (Cook Inc.) was approved for clinical use in Europe.

### Comparison of Sirolimus- and Paclitaxel-Eluting Stents

The above-mentioned trials only compared drug-eluting stents to bare metal stents. These trials have demonstrated superiority of DES to BMS, but did not allow to determine the relative efficacy of drug-eluting stents. Currently, both sirolimus- and paclitaxel-eluting stents have gained recognition and are used commercially, therefore, head-to-head trials comparing the two types of stents have become a logical next step in evaluating their efficiency.

One of such trials is a prospective, randomized, multicenter REALITY (Comparison Study of the Cypher Sirolimus-Eluting and TAXUS Paclitaxel-Eluting Stent Systems) trial of 1353 patients [41] comparing angiographic and clinical outcomes of SES and PES (Cypher versus TAXUS) placement in patients with de novo lesions in native coronary arteries 2.25 to 3.0 mm in diameter. Neointimal hyperplasia was less in the SES group ( $0.09 \pm 0.43$  mm vs  $0.31 \pm 0.44$  mm, respectively,  $p < 0.001$ ), albeit there was no difference in the restenosis rates in the two groups. Most importantly, the target vessel revascularization rates were also similar at 5.0% for the SES group and 5.4% for the PES group ( $\chi^2 = 0.8$ ). Minimal lumen diameter at 8 months was  $2.00 \pm 0.54$  mm in the SES group vs  $1.85 \pm 0.52$  mm in the PES group. However, it did not result in the significant decrease in the binary restenosis rate for the Cypher group (7.0% vs 8.3% for Taxus,  $p < 0.32$ ), as shown by the recently published SIRTAX (Comparison of Sirolimus-Eluting and Paclitaxel Eluting Stents for Coronary Revascularization) trial [42].

However, the SES treatment of ISR proved to be superior to the PES treatment. A randomized ISAR-DESIRE (Sirolimus-Eluting Stent or Paclitaxel-Eluting Stent vs Balloon Angioplasty for Prevention of Recurrences in Patients With Coronary In-Stent Restenosis) trial compared the use of balloon angioplasty with SES and PES treatment of ISR in 300 patients with restenosis after bare-metal stenting [43]. At a mean of 197 days after the stent placement repeat coronary angiography was performed in 92% of the patients. The primary end point of angiographic restenosis occurred in 44.6% of patients treated with balloon angioplasty compared with 14.3% in the sirolimus group ( $\chi^2 < 0.001$  vs balloon angioplasty) and 21.7% in the paclitaxel group ( $\chi^2 = 0.001$  vs balloon angioplasty). Although at one year follow-up there was no difference in the rates of death and MI, the need for target vessel revascularization was significantly less in patients treated with DES. In the ISAR-DIABETES (Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic

patients) trial SES also demonstrated greater efficacy compared with PES [44].

### Other Antiproliferative Agents for Stents

Everolimus is a new mTOR inhibitor drug working in the same way as sirolimus. A prospective, randomized, single-center, single-blind feasibility FUTURE-I (First Use to Underscore Restenosis Reduction with Everolimus) trial compared the everolimus-eluting Challenge stent (Biosensors International, Newport Beach, CA, USA) with a bare metal stent in 42 patients [45]. In-stent late loss was significantly lower in the everolimus group - 0.11 mm vs 0.85 mm in the BMS group ( $\chi^2 < 0.001$ ), and neointimal volume was reduced. SPIRIT-I (Comparison of a Durable Polymer Everolimus-Eluting Stent with a Bare-Metal Coronary Stent) trial confirmed the efficiency of the everolimus-eluting stent (EES) and initiated SPIRIT-II ? SPIRIT-III projects [46].

Zotarolimus - another sirolimus analog - is a pharmacological component of the Medtronic AVE ABT-578 stent. Its efficacy was confirmed by the ENDEAVOR-I and ENDEAVOR-II (Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in de Novo Native Coronary Artery Lesions) trials (restenosis rate of 9.5% vs 32.7% for BMS) [47,48].

Other agents have been experimented with in drug-eluting stents, but they have not proved as successful as the above-mentioned ones. The long-term effect of stent-based QP2 (7-hexanoyltaxol, a paclitaxel analog) delivery on coronary lesions was evaluated in 15 patients [49]. At 6 months intrastent neointimal tissue growth was 1.2 mm, and intrastent lumen loss was 0.47 mm. At 12 months, however, the intrastent luminal diameter loss was 1.36 mm, and restenosis rate was 61.5%. In the SCORE (Study to Compare Restenosis Rate Between QueST and QuaDS-QP2) trial, 266 of 400 planned patients were randomized and treated with either a QP2-covered stent, or a bare metal stent. Enrollment was stopped due to increased thromboses in QP2-stents (11.7% vs 2.2%,  $\chi^2 = 0.022$ ). At 12 months MI rate in the QP2 group was 21% vs 3% in the control group ( $p < 0.001$ ).

Another unsuccessful trial of 150 patients was IMPACT (Inhibition with MPA of Coronary Restenosis Trial) [50]. The purpose of the study was to evaluate mycophenolic acid (MPA)-eluting Duraflex stents (Avantec Vascular Corp., Sunnyvale, CA, USA) vs BMS. Mycophenolate is derived from the fungus *Penicillium stoloniferum* and is used for the prevention of kidney, heart and lung transplants rejection [51]. It inhibits the pathway of purine synthesis, which prevents lymphocyte proliferation and antibody formation. Although mycophenolate and sirolimus mechanisms differ, the former also blocks cell growth in phase G1. Angiographic analysis were performed at 6-month follow-up. There were no differences noted

between the two groups with respect to late intrastent luminal loss.

### Instead of a Conclusion

Many researchers believe that drug-eluting stents represent the third era in the development of interventional cardiology following transluminal balloon angioplasty and the implantation of metal stents [52,53]. Indeed, drug-eluting stents demonstrate high efficacy and safety. They have been successfully used in clinical practice allowing significant reduction of neointimal hyperplasia and restenosis rates while showing the same MACE rates as bare metal stents.

Although complications after DES implantation may include stent malapposition, aneurysm, or acute/subacute/late thrombosis, their rates are comparable to those after BMS placement. Populations that benefit most from DES implantation include patients with diabetes mellitus, long coronary lesions and lesions in small-diameter vessels, as well as patients who develop restenosis after balloon angioplasty or stenting, because they show significantly higher restenosis and repeat revascularization rates. Perhaps treating such patients with DES will soon become the 'gold standard'.

New types of DES are expected in the market, which will lead to increased competition and reduce their cost. However, even with a higher cost drug-eluting stents represent one of the most promising fields in interventional cardiology.

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