Drug-Eluting Stents for In-Stent Restenosis and Acute Myocardial Infarction

Present Data from Nonrandomized Studies

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Abstract

In-stent restenosis (ISR) remains the "Achilles' heel" of percutaneous stent angioplasty treatment of patients with atherosclerotic disease of the coronary arteries. Recently, drug-eluting stents (DES) have ushered in a revolution in the treatment of these patients, yet, to date, their efficacy and safety have been demonstrated primarily for native de novo coronary lesions. For ISR, intracoronary brachytherapy using β- or γ-radiation is considered the standard of care. Nevertheless, DES are used for ISR lesions in clinical practice. This review outlines the few results currently available from small observational studies and larger registries. The designs of two ongoing randomized trials evaluating the sirolimus-eluting and the paclitaxel-eluting stent versus brachytherapy in patients with ISR lesions are also presented. Patients with acute myocardial infarction (AMI) have mostly been investigated in the context of small, uncontrolled studies and registries. The incomplete evidence to date is that implantation of sirolimus-eluting stents in patients with AMI is safe and effective.

Key Words: Coronary Heart Disease · Stents · Restenosis · Acute Myocardial Infarction · Drug delivery

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Drug-eluting Stents zur Behandlung von In-Stent-Restenosen und akutem Myokardinfarkt

Zusammenfassung

Die In-Stent-Restenose (ISR) hat sich als „Achillesferse" der perkutanen Behandlung mittels Stentangioplastie von Patienten mit atherosklerotischer Erkrankung der Koronararterien herausgestellt. In jüngster Zeit haben Medikamente freisetzende („drug-eluting") Stents (DES) eine Revolution in der Behandlung dieser Patienten eingeläutet; die Effizienz und Sicherheit der DES sind derzeit jedoch hauptsächlich für native De-novo-Läsionen belegt. Für die ISR bietet sich die intrakoronare Brachytherapie mit β- oder γ-Strahlen als Therapie der Wahl an. Dennoch werden DES in der klinischen Praxis zur Behandlung von ISR eingesetzt. In dieser Übersicht wird über die wenigen bisher vorliegenden Ergebnisse von kleineren Beobachtungsstudien und größeren Registern berichtet. Des Weiteren werden die Designs von zwei derzeit laufenden randomisierten Studien zur Behandlung der ISR mit dem Sirolimus bzw. Paclitaxel freisetzenden Stent im Vergleich zur Brachytherapie vorgestellt. Ergebnisse von Patienten mit akutem Myokardinfarkt (AMI) und DES wurden bislang nur in kleineren, unkontrollierten Studien und Registern veröffentlicht. Die daher bislang noch unvollständige Evidenz weist darauf hin, dass Sirolimus freisetzende Stents bei Patienten mit AMI sicher und effektiv eingesetzt werden können.

Schlüsselwörter: Koronare Herzkrankheit · Stents · Restenose · akuter Myokardinfarkt · Pharmakologische Therapie

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Introduction

Percutaneous coronary intervention (PCI) has become the preferred treatment option for patients with de novo lesions or in-stent restenosis (ISR) – independent of their clinical setting of stable angina or acute myocardial infarction (AMI).

Each year, about 300,000 patients worldwide develop recurrent symptoms as a consequence of ISR following initially successful stent implantation. The predominant factor contributing to major cardiac events 9 ± 4 months after the intervention is the need for target lesion revascularization secondary to recurrent restenosis [18]. Repeat balloon angioplasty of ISR will yield an acceptable (~ 20%) rate of recurrent restenosis only for focal ISR. For the diffuse type of ISR (> 10 mm in length), balloon angioplasty is associated with a 35–50% incidence of target vessel revascularizations; this incidence increases to 80% in cases of in-stent reocclusion [14].

Several randomized studies have demonstrated the superiority of adjuvant intracoronary radiation therapy (brachytherapy) over conventional balloon angioplasty in the treatment of ISR [13, 19, 27, 31]. In 2002, about 50,000 cases of brachytherapy have been performed worldwide. The efficacy of this therapeutic approach has been demonstrated for coronary lesions of varying lengths and vessel sizes, in native coronary arteries as well as saphenous vein grafts, and in nondiabetic as well as diabetic patients [2, 7, 21, 29, 32]. However, intracoronary radiation therapy is subject to several limitations:

- the presence of a cardiologist, a radiotherapist (not necessarily in Germany), and a radiation technician/physicist is mandatory throughout the procedure;
- the risk of late stent thrombosis, particularly in cases of new stent implantation, is not negligible [28];
- finally, and most importantly, evidence is slowly emerging that the beneficial mid-term efficacy of brachytherapy may not be maintained in the long run after Gamma-brachytherapy [30].

Drug-eluting stents (DES) have been developed to suppress neointimal hyperplasia following stent deployment. The efficacy of the compounds sirolimus (rapamycin) and paclitaxel, released in a controlled manner off the stent from a polymer coating, has been shown for native de novo coronary artery lesions in several randomized controlled trials [4, 15, 16, 22, 24]. DES may also turn out to be an attractive alternative to brachytherapy in the treatment of patients with ISR.

In patients with AMI, routine stent implantation has been shown to have a better procedural success rate and clinical outcome than balloon angioplasty [23]. However, restenosis and vessel reocclusion remain major challenges limiting the long-term success of percutaneous treatment [6]. Animal experimental studies suggest that thrombotic material upon coronary artery stenoses increases the risk of neointima formation [10]. In a clinical study of 400 patients with stent implantation in AMI, angiographic restenosis occurred in 31%, considerably more than expected for patients with stable coronary disease [17].

To date, DES for the treatment of ISR and in patients with AMI have mostly been investigated in the context of small, uncontrolled studies and registries. It is the purpose of this paper to summarize these results.

In-Stent Restenosis

To assess the safety of the sirolimus-eluting stent (SES) in the treatment of ISR, 41 patients with ISR in native vessels 2.5–3.5 mm in diameter have been studied in São Paulo, Brazil (n = 25), and Rotterdam, the Netherlands (n = 16) [1]. The lesions were covered with a maximum of two 18-mm stents, and patients were discharged on a regimen of aspirin (325 mg/d indefinitely) and clopidogrel (75 mg/d for 2 months). Focal and diffuse ISR were present in 40% and 60% of São Paulo patients and 19% and 62% of Rotterdam patients, respectively. Chronic total occlusions were present in the remaining 19% of Rotterdam patients. Three Rotterdam patients presented with ISR following failed intracoronary brachytherapy. Quantitative coronary angiography in the 25 São Paulo patients revealed an increase of late luminal loss from 0.07 mm at 4 months to 0.35 mm at 1 year, corresponding to a decrease in minimum lumen diameter from 2.65 mm to 2.50 mm, respectively. At 1 year, one patient had developed a recurrent restenosis, but there were no deaths, myocardial infarctions (MIs) or target lesion revascularizations. These results contrasted with those observed in the 16 Rotterdam patients in whom event rates were 12.5% (restenosis), 12.5% (death), 6.3% (MI), and 12.5% (target lesion revascularization).

Similar results have been reported for the paclitaxel-eluting stent. The single-arm, two-center TAXUS III Trial evaluated the paclitaxel-eluting Taxus NIRx® stent for the treatment of ISR in 28 patients with lesions ≤ 30 mm in vessels between 3.0 and 3.5 mm in size [25]. Focal, diffuse and totally occlusive ISR were present in ten patients (36%), 17 patients (61%) and one patient (4%),

respectively. Two stents per lesion were implanted in 13 patients (46%). One patient sustained a non-Q-wave MI within 30 days. At 1 year, there were no deaths or Q-wave MIs; one patient had undergone coronary artery bypass grafting and six patients (21%) a repeat target vessel revascularization procedure.

The international, internet-based, e-CYPHER Registry was established in April, 2002, as a post-marketing surveillance tool to assess the performance of the SES in a "real world" scenario. Up to 15,000 patients will be enrolled in this registry. By February 2004, > 12,000 patients had been entered at 60 centers worldwide and almost 2,000 of these patients were treated for ISR. Six-month follow-up data is expected to be available by the end of 2004. Also in April 2002, the Rotterdam University Hospital Thoraxcenter established implantation of the SES as the default strategy for all PCIs as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) Registry. By October 2002, 508 consecutive patients had been enrolled, including 67 patients (13%) with ISR of whom 17 (25%) presented with recurrent restenosis after failed brachytherapy, 36 (53.7%) had focal disease, and 31 (46.3%) had diffuse disease or a total occlusion. At 1 year, there were no deaths, 1.8% of patients experienced MI, and 12.3% of patients had to undergo repeat target lesion revascularization [9].

Other registries on the SES exist in Marseille, France, and Germany. Barragan et al. recently reported on 332 consecutively treated patients (41% diabetics) with a total of 436 ISR lesions, of which 99% were located in native coronary arteries (update on [3]). The mean implanted stent length was 20 mm, with 76% of stents implanted without predilatation. There were no subacute stent thromboses, and two patients (0.6%) died of cardiac causes within 30 days. six-month follow-up obtained in 251 patients (75.6%) with 326 lesions disclosed seven incidences (2.8%) of target lesion revascularizations and an overall MACE (major adverse cardiac events) rate of 4.0%. At 12 months (142 patients [42.8%]/190 lesions), rates of target lesion revascularizations and MACE increased to 11.3% and 13.4%, respectively. In November 2003, Hamm et al. presented initial results from the German CYPHER Registry, which, by then, had enrolled 3,239 patients (3,525 lesions), with 790 patients (24%) treated for ISR. Six-month follow-up in 337 (43%) of the latter patients revealed incidences of death, MI, coronary artery bypass grafting, and repeat percutaneous intervention of 0.6%, 0.6%, 0.3%, and 4.5%, respectively (update on [8]).

The SECURE Registry was established in March 2002 at five investigational sites in the USA to collect information on a total of 250 patients at high risk for restenosis and failed previous intervention. All patients are treated with SES implantation under a compassionate-use protocol. By September 2003, 202 patients were enrolled [26]. Of these patients, 146 (72%) had failed previous intracoronary brachytherapy, whereas the other 56 patients had ISR without previous brachytherapy. At a mean follow-up of 4.8 months, MACE had occurred in 18 patients (12.3%), and 17 patients (11.6%) had undergone repeat target lesion revascularizations. These incidences tended to be higher but were statistically not different from those observed in patients without previous brachytherapy (8.9% and 5.4%, respectively).

Treatment with DES appears to be safe, at least in patients who have not undergone previous brachytherapy. The long-term outcomes of DES treatment of ISR cannot be judged with confidence. Possibly, they are worse in patients with complex ISR, particularly after failed brachytherapy.

It is unclear if the adjuvant pharmacological therapy as used for the treatment of de novo lesions is sufficient for ISR lesions. Moreover, no direct comparisons between the acknowledged standard of care for ISR, namely, intravascular brachytherapy, and DES are available.

The paucity of data contrasts with the frequent use in clinical practice of DES for ISR lesions, as evidenced by the German CYPHER and the international e-Cypher Registries. The nonavailability of brachytherapy is insufficient substantiation for the use of DES in the context of ISR. It is unlikely that registries will provide enough information on the efficacy of DES for ISR treatment, even if large patient numbers are enrolled. The quality of data cannot be compared with that of randomized trials. Systematic monitoring of data entry is lacking, patients are often not enrolled consecutively, and quantitative coronary angiography by an independent core lab as well as adjudication of clinical events by an independent committee are usually not performed. Therefore, randomized controlled trials are imperative. However, given these restrictions, the results achieved with DES in the treatment of ISR are promising.

Results to be Expected from Randomized Controlled ISR-Trials

The relative value of DES and brachytherapy in the treatment of ISR can be determined with confidence

only in the context of a randomized controlled trial. Two trials addressing this issue are currently ongoing.

SISR (Sirolimus-eluting stent for In-Stent Restenosis). This study involves 26 US centers and will enroll 400 patients with ISR in native coronary arteries (2.5–3.5 mm), randomized to SES or vascular brachytherapy (50% β- and 50% γ-radiation) in a 2 : 1 ratio [9]. An ISR length of 15–40 mm is required for study inclusion. The key exclusion criterion is prior (β- or γ-) brachytherapy. The primary endpoint is target vessel failure at 9 months, among the secondary endpoints are binary angiographic restenosis at 6 months, as well as target lesion and target vessel revascularization at 9 months. Patient recruitment is expected to be concluded in 2004.

TAXUS V – ISR. The slow-release formulation paclitaxel-eluting stent for the treatment of ISR will be evaluated prospectively and in a 1 : 1 randomized fashion against β-radiation in the TAXUS V – ISR Trial. This trial, which involves 40 centers, is designed to enroll 488 patients with ISR < 46 mm in vessels between 2.50 and 3.75 mm. Again, the primary endpoint is target vessel failure at 9 months. All patients will undergo control angiography at 9 months, with 250 patients scheduled for an intravascular ultrasound investigation at 9 months.

Acute Myocardial Infarction

There is very little information available as to the efficacy and long-term safety of DES in AMI. This part reviews the major results from the Rotterdam Research Registry [11, 20] and shows which results are to be expected within this year from randomized trials (Cypher-AMI, Typhoon).

Lemos et al. [11] evaluated the early outcomes of patients with acute coronary syndromes treated with SES. In the single-center RESEARCH Registry 198 patients that had been treated exclusively with SES were compared with a control group of 301 consecutive patients treated with bare stent in the same time period immediately before the registry began. The incidence of MACE during the 1st month was evaluated (death, MI, reintervention). Compared with control patients, patients treated with SES had more primary angioplasty, more bifurcation stenting, less previous MI and less glycoprotein IIb/IIIa inhibitor use. The 30-day MACE rate was similar between groups, and in multivariate analysis, SES utilization had no influence on MACE. Thus, this registry provides information that SES implantation in patients with acute coronary syndrome is safe. However, with the focus on a 30-day endpoint it cannot and does not provide information that SES implantation is superior to bare stent implantation in terms of reducing restenosis.

Saia et al. [20] report from the same registry about 96 patients with ST-elevation AMI (STEMI) of whom 92.7% underwent PCI within 12 h after the onset of symptoms. Postprocedural TIMI-3 flow was achieved in 93.3% of patients. In-hospital mortality was 6.2%, one patient had reinfarction and reintervention on the 1st day. During follow-up (mean 218 days) one patient died (1.1%), there were no re-MIs, late thromboses, or reinterventions. At angiographic follow-up (70% complete), no patient presented with restenosis, late loss was -0.04+/-0.25 mm. Thus, in this registry, SES implantation in patients with STEMI was safe without documented angiographic restenosis at 6 months. Results of patients with STEMI and NSTEMI from the German Cypher Registry, begun in April 2002, will be available later this year. The registry collected 1,638 patients during the 1st year of whom about 10% had STEMI and 7% NSTEMI.

In a recently published registry, primary angioplasty was performed with SES in 186 consecutive AMI patients who were compared to 183 patients treated with bare stents [12]. Postprocedural vessel patency, enzymatic release, and the incidence of short-term adverse events were similar in both the sirolimus and the bare stents (30-day rate of death, reinfarction, or repeat revascularization: 7.5% vs. 10.4%, respectively; p = 0.4). Stent thrombosis was not diagnosed in any patient in the sirolimus group and occurred in 1.6% of patients treated with bare stents (p = 0.1). At 300 days, treatment with SES significantly reduced the incidence of combined adverse events (9.4% vs. 17%; hazard ratio [HR] 0.52; p = 0.02), mainly due to a marked reduction in the risk of repeat intervention (1.1% vs. 8.2%; HR 0.21; p = 0.01)

Results to be Expected from Randomized Controlled AMI-Trials

Granatelli et al. [5] report about a small randomized trial comparing SES (n = 18) with bare stent (n = 15) in patients with STEMI treated within 24 h of symptom onset. Abciximab was used in 97% of cases. There were no in-hospital events, and angiographic 6-month follow-up is still to be presented in final form. The study is of special interest, because of the three patients in the SES group who stopped ticlopidine early (prior to 6

months), two experienced late stent thrombosis. Thus, there may be a requirement for longer treatment with clopidogrel/ticlopidine in patients receiving SES in AMI.

Cypher-AMI is a larger (n = 124), two-center (University of Freiburg, Heart Center Bad Krozingen, Germany) randomized trial comparing angiographic late loss and incidence of restenosis for the SES „Cypher" to bare stent in patients presenting with STEMI or NSTEMI within 24 h of symptom onset. Clinical endpoints will be analyzed, however, the study is powered only for the angiographic endpoints. All patients have been recruited, and 6-month follow-up angiography is to be completed in Febuary 2004. Thus, the first angiographic results from an adequately powered randomized trial will be available in the spring of this year.

Typhoon is an even larger trial (n = 700) aiming at comparing clinical endpoints in STEMI patients randomized to either SES or bare stent. An angiographic follow-up substudy at 6–8 months will allow correlation of clinical and angiographic results. Recruitment is well under way, and final results are expected by the end of this year.

Perspectives

It is conceivable that the DES may be more efficaciously and cost-effectively used than brachytherapy in specific types of ISR, such as lesions that can be covered with a single stent. In diffuse ISR that needs to be covered with more than one stent as well as ISR in insulin-dependent diabetics, the DES may be as efficacious but less cost-effective or even less efficacious than brachytherapy. Most probably, brachytherapy will remain an indication in a few selected cases. In what way future patients will be assigned to either mode of therapy is in need of urgent clarification, in order to position the currently practiced use of DES for the treatment of ISR in an evidence-based context. The results of ongoing randomized trials and larger registries will allow us early next year to make evidence-based decisions about which stent to use in patients with AMI. The incomplete evidence to date is that implantation of SES in patients with AMI is safe and effective.

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