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

Zusammenfassung

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 adjutant 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%),