

41. THE QUANAM QUADDs-QP2 STENT

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Background and rationale

The concept of delivering — or eluting — a drug from a stent over a period of time to treat the problem of in-stent restenosis following stent implantation is an attractive strategy. Local drug delivery for cardiovascular disease, prior to the advent of stents, was restricted to catheter-based delivery. These technologies were limited by the compounds available for catheter-based delivery, dwell time of the delivery catheter and length of residence time of these compounds in the vessel wall following completion of the delivery. Stent-based drug delivery offers a platform for not only maintaining compounds directly at the site of injury or disease and providing prolonged delivery, but it also allows for the delivery of hydrophobic compounds which cannot be easily delivered via conventional methods.

The stent platform

The QuaDDS-QP2 stent is based on the uncoated QueST stent platform (formerly Quanam Medical Corporation) The QueST stent is laser cut from one continuous piece of 316L stainless steel tubing and does not require subsequent welding or joining. The slotted tube stent is premounted on an over-the-wire polyethylene balloon. The QueST consists of individual segments, each 3.8 mm long, connected by inter-segment connecting links (Figure 41.1). The shaft of the delivery system is coaxial over the distal section and compatible with a 0.014 inch guidewire. The stent delivery system has two radiopaque (platinum) markers.

Description of eluting coating

The QuaDDS stent is a QueST stent covered with a series of 2 mm (width) polymer sleeves made from an acrylate polymer and formed into ringed sleeves (Figure 41.1). The sleeves have a thickness of approximately 0.0025 inch (half the thickness of a stent strut). The stent length determines the

number of sleeves which are placed equidistant from each other over the length of the stent to prevent total stent coverage. For example, a 13 mm stent length would carry four sleeves. The non-biodegradable proprietary polymer sleeve is loaded with the microtubule stabilizer 7-hexanoyltaxol, also referred to as QP2. QP2 is loaded into the polymer sleeve by dissolving the drug into a solvent that absorbs into and swells the polymer. The polymer absorbs a specified volume of the solution at a known concentration. The solvent is subsequently removed by vacuum drying. The total dose per sleeve is approximately 800 μg . Therefore, the 13 mm stent carries 3.2 mg and the 17 mm stent a dose of approximately 4.0 mg of QP2.



Figure 41.1: The Quanam QueST stent consists of individual segments each 3.8 mm long joined by inter-segment connecting links. On the QuaDDS-QP2 stent a non-biodegradable proprietary polymer is ensheathing the QueST stent loaded with the slow-release microtubular inhibitor 7-hexanoyltaxol ('taxen').

Molecular action of drug

Quanam has evaluated a number of drugs for their effectiveness in minimizing restenosis after stent placement in non-atherosclerotic rabbits and pigs. Of the drugs evaluated, paclitaxel showed a positive effect in reducing neointima. However, the desire to extend drug retention for a longer period of time than that of paclitaxel, the more hydrophobic derivative of paclitaxel, 7-hexanoyltaxol (QP2, called a 'taxen') became the focus of investigation [Kingston 1991]. The mechanism of activity is similar to that of paclitaxel, in that it inhibits microtubule formation by inhibiting microtubule depolymerization thus interfering in the cell cycle at the the G2/M phase. QP2 is about half as soluble as paclitaxel, which has a solubility of 1 $\mu\text{g}/\text{ml}$.

Elution profile

In vivo drug release studies in a rabbit iliac model have demonstrated that approximately 80% of QP2 is released within the first 90 days following a

continuous sustained release profile with the drug still being released at 180 days. Tissue retention was maintained at a relatively constant level over a 90-day period with the drug being identified in arterial tissue at 180 days. The amount of QP2 either 1 cm proximal or distal from the stent edge was determined to be 1/10 to 1/100 of the amount found in the tissue within the stented segment. There was no detectable drug in the other tissues investigated. This indicates that under the experimental conditions, QP2 remains confined to the local area underneath the stent and immediately adjacent tissues.

Preclinical data

Both rabbit iliac and porcine coronary models have been utilized in the preclinical evaluations of the QuaDDS-QP2 stent. Doses of 1500 and 3200 μg have been evaluated at 4 and 8 weeks. A significant reduction in neointimal thickening in the absence of thrombus, acute inflammation, fibrosis, foreign body reactions, medial thinning, IEL and EEL disruptions was found. Chronic inflammation was minimal, cellular necrosis was mild to moderate, and the presence of granulation tissue was also minimal.

Clinical data

In the first clinical study (open, randomized, single-center) with the QuaDDS-QP2 stent, 14 QuaDDS-QP2 stents were implanted in 13 patients and 18 control bare QueST stents in 14 patients [Grube *et al*, 2000, 2001]. Stent sizes were 3.0 and 3.5 mm diameter with stent lengths of 13 mm and 17 mm. After 18 months, the binary restenosis rate in the coated stent group was 0% as compared to 54% in the control group. MACE after 18 months was 0% in the drug stents and 15% in the control group. The 2-year follow-up data showed no binary restenosis with an TLR of 0. Thus, the implantation of the QuaDDS-QP2 stent was extremely efficient with no side-effects (MACE =0). IVUS data revealed only minimal amount of neointimal proliferation [Honda *et al*, 2001].

The SCORE trial:

The SCORE trial (Study to COmpare REstenosis rate between QueST and QuaDDS-QP2) was the first randomized, multicenter trial with the QuaDDS-QP2 stent. The primary endpoint was target vessel revascularization (TVR)

with an anticipated reduction in restenosis rate to < 20% as compared to an expected restenosis rate of 24% to 42% seen with traditional stainless steel stents. Sample size calculated to support this goal was 400 patients from 17 sites in Europe and Australia (Principal Investigator: E. Grube). Inclusion criteria were: de novo lesions in native coronary arteries and a narrowing of $\geq 50\%$ and $\leq 100\%$ with reference diameters between ≥ 3.0 mm and ≤ 3.5 mm. Implanted QuaDDS-QP2 stents were either 13 mm or 17 mm long, the target lesion length had to be suitable for stenting with a single Quanam stent. Predilatation before stent implantation was a mandatory part of the protocol, and ticlopidine/clopidogrel was prescribed for 6 months.

Interim analysis of safety outcomes led to termination of the study. At that time 266 evaluable patients were enrolled (127 drug eluting stent and 139 control). Specifically, there was no stent thrombosis in the control group and a 5.5% stent thrombosis rate present in the QuaDDS-QP2 group (95% confidence interval 3.5–7.5). There was also an increase in periprocedural myocardial infarctions that were usually related to side branch occlusion caused by the polymer bands (although lesions involving a side branch > 2.0 mm was one of the exclusion criteria). MACE at 30 days was 10.2%, predominantly due to subacute stent thrombosis and myocardial infarction. The events could not be attributed to a single underlying cause including protocol violations (like absence of predilatation). The duration of treatment with ticlopidine/clopidogrel was extended from 6 months to 1 year in patients with the active stent.

A full interim evaluation of 6 month angiographic results and clinical efficacy is underway with planned results in November 2001. Nevertheless, interim results from the IVUS substudy show that of the patients evaluated at follow-up (54 QuaDDS-QP2 and 52 controls) there were no significant differences in baseline IVUS parameters including stent expansion. There were promising and significant decreases at follow-up in MLA loss and neointimal area consistent with a reduction in neointima formation.

Upcoming clinical trials

For the time being, no further studies are planned with the QuaDDS-QP2 stent.

Future aspects

The preliminary data from the SCORE trial demonstrate the proof of principle for stents coated with antiproliferative drugs. It also points to the

need for diligent preclinical dosing studies to minimize the potential for both acute and subacute events. Because of the similar histological changes observed with both brachytherapy and taxol-eluting stents a more aggressive use of antiplatelet therapy seems mandatory after both treatments [Silber *et al.* 2001]

References

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