Coronary Restenosis; A Shifting Paradigm

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Coronary restenosis; a shifting paragdigm

Coronaire restenose; een verschuivend paradigma
(met een samenvatting in het Nederlands)

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Aan mijn ouders

Voor Mylène

CONTENT

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General Introduction and Outline of the Thesis

INTRODUCTION

Cardiovascular disease is still the main course of death in the western world [1]. Predominantly this is caused by atherosclerotic disease leading to coronary artery stenosis, occlusions and thrombo-embolic events causing infarctions and death [2].
Although coronary artery bypass grafting (CABG) has proven to be a relative safe and efficacious treatment for coronary artery stenosis, the steep rise of percutaneous coronary interventions (PCI) over the recent two decades has put the latter therapy as first choice treatment for both physicians and patients when invasive treatment is needed .Especially the availability of smaller, better deliverable and therefore more user friendly stent delivery systems has probably been the key-factor in the current success of PCI's worldwide [3–5].
However PCI is still hampered by two limitations: restenosis and stent thrombosis [6].
Restenosis is the narrowing of the coronary vessel wall after PCI and is the result of an exaggerated healing response after trauma caused by the PCI. This usually leads to recurrence of symptoms requiring re-PCI or target lesion revascularisation (TLR). The risk factors for restenosis are small vessels, long lesions, total occlusions, bifurcation lesions, diabetes and restenotic lesions. Despite the fact that the incidence of instent restenosis has decreased in recent years, in predisposed (see above) subgroups of patients and lesion subsets, restenosis rates can still be as high as 25-30 %. The treatment and prevention of coronary and in-stent restenosis has been prominent over the past decade and has lead to several revolutionary therapies varying from intracoronary brachytherapy [7], modified technical treatment options for specific lesions [8] , new stent technologies such as drug eluting stents [9], and thin strut cobalt chromium designs [10] to drug eluting balloons [11] .
All these new techniques have lead to an avalanche of pre- and clinical studies and hence new approaches and technical adaptments in coronary interventional catheterization labs worldwide (this thesis).

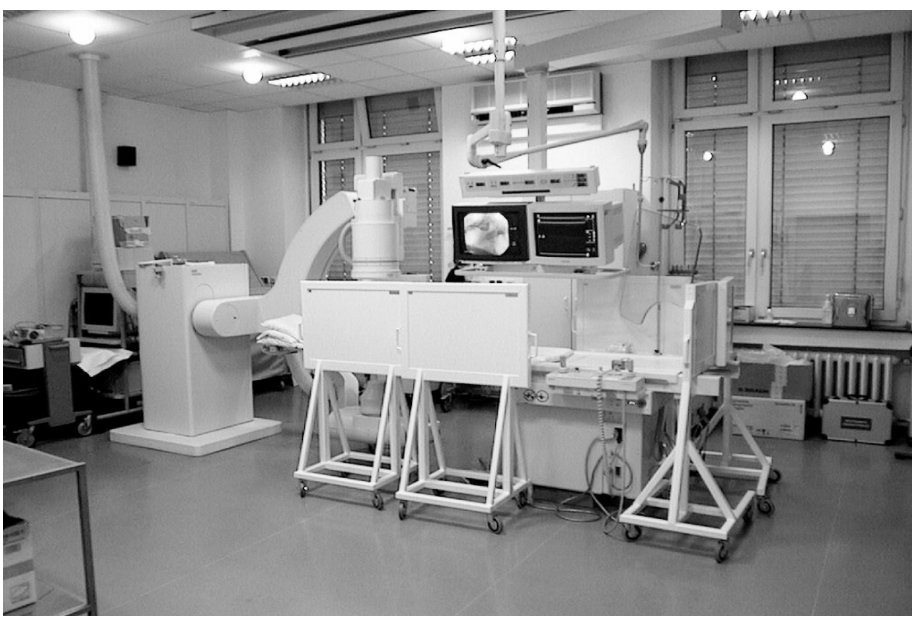
Aim and outline of the thesis

This thesis addresses three major fields of research regarding efficacy and safety of alternative treatment options in order to prevent restenosis over the past 8 years.

First the clinical use of intracoronary brachytherapy (both beta and gamma), including a first worldwide comparison against a DES. Second, various techniques for the treatment of coronary bifurcation lesions and third, the rationale of drug eluting balloons with new cobalt chromium stent designs for the prevention of restenosis.

Late nineties, a well known and proven therapy from the oncology world was introduced into the cardiology catheterization laboratories, namely brachytherapy.

Brachytherapy had shown to be very successful in treating solid tumors and other neoplastic diseases. The concept was that it could have the same beneficial effect on the excessive growth of neointima within the coronary arteries by inhibition of vascular smooth muscle cell migration and proliferation [12-15]. Immediately there were two options to choose from; beta and gamma radiation sources. The beta sources presenting the less penetrating radiation form whereas the gamma radiation was more penetrating and required an enormous amount of additional shielding into the cathlab for the purpose of staff protection (picture)



The preference –for practical reasons- hence was soon for beta radiation, however the dosimetry calculations for this therapy was much more elaborate due to the less penetrating nature of the beta radiation. Furthermore, one had to keep track of daily source decay, vessel diameter and centering of the radioactive source into the middle of the vessel lumen. In favor for beta therapy were the relative short dwell times (<3-7 minutes) in the coronary vasculature. With gamma radiation, the dosimetry calculations and source location into the vessel lumen were less elaborate, but usually much longer dwell times (15-25 minutes) were common. Commercially sophisticated devices were soon available, but came with a high price. At the early phases of intracoronary brachytherapy (ICBT), our department of interventional cardiology made the choice to study a relatively easy accessible and deliverable system with the Rhenium 186 radioactive liquid filled PCI balloons, provided by Mallinckrodt™ - St Louis, USA. The theoretical benefits involved the beta radiation source, requiring no additional shielding and automatic centering within the vessel lumen because it was delivered by means of a PCI balloon. Last but not least this approach was less expensive because no sophisticated machinery was required for delivery other than the hands of the radiation oncologist and interventional cardiologist. The latter being also the downside because heavy leaden gloves were required when inserting the balloon into the guiding catheter, making accurate manipulations more difficult. However this form of therapy was hampered by the enormous difficult logistics involved. Production, transport and final assessment of source activity proved to be too complicated for routine practice. Later at follow-up it became also clear that due to an unknown phenomenon called "edge effect" (fall of off radiation dose combined with barotrauma form the balloon) there was a progression of neointimal tissue growth exactly at the borders of the previous balloon inflation later named the "candy wrapper " by Dr. Remo Albiero in Milan [16].

We then decided to investigate the potential of having the first (and eventually only) worldwide randomized prospective pilot study comparing beta versus gamma ICBT, called the BEGUT (BEta versus Gamma Utrecht Trial). However, already during study enrolment a new promising device to prevent and treat restenosis became available: a drug eluting stent called Cypher© by Cordis J&J. Although the results with ICBT were quite good (reduction of restenosis > 50 %) it became clear that the logistics involved in this treatment modality

were cumbersome and besides several new complications occurred such as geographical miss (zone with barotraumas by stent or balloon, but not treated with ICBT) and also sub- acute thrombosis (> 5-15 %), which was unexpected and new at that time and lead to a prolongation of dual antiplatelet therapy. The descision was made to add a third treatment arm to the BEGUT with Cypher stents. Very soon it became clear that not only the DES was much more user and patient friendly but also resulted in better clinical results. This lead quite abruptly to the end of ICBT worldwide.

Meanwhile, another study was performed called the OPTIRAD (Optimal Timing for RADiation) where 60 patients underwent immediate versus delayed ICBT in a randomized way by using the radial access for PCI and immediate treatment followed by ICBT two days later via the groin in patients randomized to the delayed treatment arm. This because of early animal work performed by Waksman etal –at Emory, Atlanta Georgia, where delayed ICBT seemed to have a better result at follow-up, probably by simply "hitting" more vulnerable smooth muscle cells which were starting to proliferate after previous balloon trauma 48 hrs earlier [17]. Needless to say that this study again involved very careful planning and coordination.

During the years 2002-2004 it became obvious that there was no stopping to the DES anymore and a widespread use of several different DES became common. Based on pricing but also concern on the long term effect of this permanent implant we were cautious in Utrecht to adopt this therapy in all patients and decided to work more with new bare metal stent designs with thinner struts and more flexibility and deliverability promising less trauma and therefore less restenosis in the long term. By 2006 it became clear that the new DES – era came with a price (late stent thrombosis) and that the new TSCC (Thin Strut Cobalt Chromium stent) indeed provided an easier stent deliverability and less clinical restenosis compared with the older bare metal stent generation and was not penalized by late and very late stent thrombosis problems [18].

Over the past three years our focus has been on a potential combination of the best of two worlds; a DES with a fully degradable polymer and TSCC stent platform. Besides this theoretical ideal combination we also studied a new device which promises to reduce the costs involved in multi-Des stenting by customizing the length of the required stent

in –situ and being able to treat 2-3 lesion with the same device ; the Custom NX® device by Xtentinc™.

However, although new DES and TSCC provided less restenosis, some specific patient groups still presented with higher restenosis rates than others; coronary bifurcation lesions. Probably due to a combination of technical difficulties during treatment requiring more wires, balloons and handling – hence more trauma to the coronary artery wall - than in a regular single lesion straightforward PCI, especially the sidebranches still have a 15-30 % restenosis rate in most studies [19-20]. The use of DES has not changed that figure and even lead to a rise in late stent thrombosis numbers potentially due to crushing of polymers and uncontrolled drug release when two stents were used in a bifurcation.

Our attention at first was focussed on simplifying the stent techniques for bifurcations called the Modified T (or Utrech-'T') technique. Currently a new promising approach, involving less stenting is being studied with the use of DEB (drug eluting balloon) in bifurcations called the DEBIUT (Drug Eluting Balloon in bIfUrcations Trial). Interestingly a lot of the older issues involved with the original Rhenium 186 RadioCath balloons are now re-used because edge effect, geographical miss and late thrombosis are again potential side effects of the DEB. However the big difference now is that we have learned from the past and know how to deal and prevent these potential complications [21]. This makes the circle in the clinical battle against restenosis during the past 10 years perfectly round again.

For the future we believe there will be new therapies and new devices and have high hopes for the combination of TSCC, DES, biodegradable polymers on a totally biodegradable stent platform, where now the first preliminary studies are starting [22]. This should lead to the ideal " leave no footprint " concept. One has to bear in mind however that although we have taken very important steps in the past decade, all we do is simply treating symptoms. The cure for the disease called atherosclerosis is still not found and will require many years of basic science and clinical research and will probably involve oral medication, stem cells, gene therapy with local drug delivery platforms by balloons and stents.

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2

Coronary Radiation Therapy with Liquid Rhenium-186; A First Clinical Experience.

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ABSTRACT

Background

Coronary radiation therapy (CRT) is a new, attractive approach for treatment and prevention of restenosis after percutaneous coronary interventions (PCI). The RadioCath™ device consists of a standard balloon dilatation catheter that can be charged with a solution of sodium [^{186}Re]perrhenate, a predominant beta emitter. The safety and performance of this new device was evaluated in a pilot trial.

Methods and Results

Thirty three patients with a de novo lesion in a native coronary artery were treated with the RadioCath™ device, after successful angioplasty. The average dwell time to deliver a dose of 20 Gy at 0.5 mm into the vessel wall was 418 ± 64 seconds. The treatment was well tolerated by most of the patients. In 79% of them only one inflation cycle was required to deliver the prescribed dose. There were two procedural, device-related complications (5.9%) and three, minor procedural related in-hospital complications (9%).

Conclusions

CRT using a balloon catheter device, charged with a sodium [^{186}Re]perrhenate solution, seems feasible and safe. Clinical and angiographic 6 month follow-up data are pending.

Key words: Coronary revascularization, angioplasty, radiation therapy, liquid filled balloon, radioisotopes

INTRODUCTION

Restenosis remains a major limitation of PCI. It is a complex phenomenon that can be divided into three major reactions which, to a certain extent, always occur after injury: elastic recoil of the vessel wall, remodeling of the artery and tissue proliferation into the lumen of the artery. (1)

Depending on the definition, restenosis becomes significant in 30 to 50 % of the patients treated with a PCI. (2,3)

Recoil and remodeling of the vessel wall after the intervention can be prevented by implantation of a coronary stent. (4) But coronary stents do not prevent neo-intimal proliferation. In contrary, permanent implantation of a metallic stent stimulates tissue proliferation through a foreign body reaction.(5)

CRT is one of the new strategies under investigation in the treatment and prevention of restenosis after PCI. In principle, it is an attractive approach, since, by using coronary stents, the problem of restenosis is limited to a proliferative disorder.

In other areas of medicine, like in dermatology, the treatment of abnormal scar formation using local irradiation is known to be very effective.

The first experimental and clinical experiences with CRT were not always positive. (6,7) Many obstacles need to be overcome before this technique can become the first choice approach in restenosis treatment. The ideal system to deliver radiation needs to be determined (beta vs. gamma sources, catheter- vs. stent-based technology or intravascular vs. external beam radiation). Which isotope has the ideal characteristics for this application, what is the therapeutic window, what are the long-term effects, and which lesions will benefit most from the treatment (de novo or restenotic lesions)?

CRT has also created new problems, such as the 'edge effect' or the recurrence of the stenosis at the borders of the radiated and injured segment, particularly seen with beta-particle emitting stents, and the increased incidence of late thrombotic complications, particularly when combined with additional coronary stenting. (8-13)

At present, only intra-coronary radiation using a gamma source, like an iridium-192 wire or ribbon, has been proven to be effective in patients with aggressive, recurrent restenosis, especially diffuse in-stent restenosis .(14-20)

This paper reports the first clinical results of a pilot study in post-angioplasty patients with a new device, consisting of a simple balloon dilatation catheter that can be charged with a sodium [^{186}Re]perrhenate solution.

METHODS and RESULTS

The Radiation Treatment Balloon Catheter Device (RadioCath™)

The RadioCath™ device consists of four components: a radiation treatment balloon (RTB) catheter with a balloon length of 25mm; a manifold, containing a shielded vial with a clear, colourless sodium [^{186}Re]perrhenate solution, and an inflation device. (Figure 1) Rhenium-186 is a predominant beta emitter (92.2%). The maximum energy of the beta particles is 1.077 MeV. It has also a limited gamma ray emission, the most abundant (9.5%), with an energy of 137 keV. The isotope has a half-life of 3.78 days. The device is designed and provided by Mallinckrodt Inc., St. Louis, MO, USA.

Following successful PTCA, the RTB catheter is positioned across the target lesion. Before charging, all air is withdrawn from the RTB catheter by creating a vacuum for thirty seconds with a 30 ml stop-lock syringe. The RTB is then charged with a solution of rhenium-186 in the form of sodium [^{186}Re]perrhenate (250 mCi/ml), by inflating the balloon at a pressure of 5 atmospheres. The dwell time to deliver 20 Gy at 0.5 mm into the vessel wall, targeting the adventitia, varies from 5 to 10 minutes, depending on the size of the artery and the specific activity of the solution.

During the inflation the artery is totally occluded at the target lesion site. Depending on the patients' tolerance, sometimes several inflation-deflation cycles are required to achieve the prescribed dose of 20 Gy.

Once the RTB is positioned and charged, the part of the catheter outside the patient is shielded with a mobile plastic shield, which absorbs nearly all the beta particles. A special developed valve system inside the manifold prevents leakage of radioactive solution back into the inflation device.

During the procedure the radioactivity is measured regularly at the patients' chest and at different parts of the device. A blood sample is taken before and after the procedure and analysed by measuring its radioactivity in a 4-in. NaI (Tl) scintillation detector coupled to a multi-channel analyser (Wallac, Turku, Finland). In this way, even the smallest spill of radioactive solution into the patient can be detected.

After the treatment the RTB catheter is removed from the patient by the use of plastic clamps and put into a lead container.

Study Design

The primary objectives of the study were to evaluate the safety and the performance of the RadioCath™ device. Efficacy in preventing restenosis was a secondary objective.

In total, 35 patients with a symptomatic, de novo lesion in a native coronary artery, scheduled to undergo a standard PTCA procedure, were included. Other inclusion criteria were a target lesion length ≤ 15 mm and a vessel diameter between 2.5 and 4.0 mm.

Patients with severe recoil or dissection after the PTCA that needed immediate, bail-out stent implantation, patients with a recent myocardial infarction within 72 hrs, with diffuse disease distal of the target lesion, with a bifurcated lesion, or with a left ventricular ejection fraction < 30% were excluded.

The radiation treatment was started immediately after successful PTCA, defined as a residual diameter stenosis ≤ 35%. In case stenting was indicated, this was done after the radiation treatment, to avoid shielding by the stent struts and eventual damage to the RTB catheter. Quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) were done at baseline, at the end of the procedure and at 6 month follow-up. Clinical follow-up will continue for three years.

RESULTS

From the 35 patients that were included 33 (94%) were treated with the RadioCath device. One patient was withdrawn because of a severe, occlusive dissection after PTCA that needed immediate stent implantation. Further in-hospital course of this patient was uneventful. In a second patient there was a technical failure of the inflation pressure monitoring system and the procedure was prematurely stopped, before the RTB was adequately charged.

Of the 33 patients treated, there were 19 males (58%) and 14 females. The mean age was 63 years ± 9 years. In *8* patients the LAD was the target vessel, in 11 the left circumflex and in 14 the RCA. Fourteen lesions (42%) were located in the proximal part of the vessel, 11 (33%) in the mid-portion and 8 (24%) in the distal part. The target vessel reference diameter was 2,97 ± 0.58 mm. The average baseline diameter stenosis of the target lesion was 70.6 ± 14.9 %, and the average baseline minimal lumen diameter (MLD) was 0.73 ± 0.44 mm. The residual stenosis of the target lesion at the end of the procedure was 18.3 ± 12.7 %, and the MLD was 2.12 ± 0.70 mm. (Table 1) The average acute gain after the intervention was 1.34 ± 1.11 mm. Stents were implanted in 23 patients (70%).

The average dwell time was 418 ± 64 sec. and in 79% of the patients the treatment was given in a single inflation cycle. In 15% of the patients two inflations were required and in 6% three. The average diameter of the RTB was 3.0 ± 0.3 mm.

There were only two (2/34) device-related complications (5.9%). As mentioned above, one patient was not irradiated because of a technical failure of the inflation system. In another patient an external spill of radioactivity was detected at the end of the procedure, at the proximal part of the RTB catheter shaft, outside the patient. A detailed examination showed a tear in the shaft of the RTB catheter, probably caused by manipulation using metal tongs instead of the prescribed plastic clamps. Because of the early detection of the spill, the additional radiation exposure to the patient and the operators was negligible. Further in-hospital course of this patient was uneventful.

There were no procedural related major complications. Three patients (9%) suffered a minor complication. In one patient a small, post-procedural rise in creatinin

phosphokinase (1.5 times the upper limit) was detected, two other patients experienced a groin hematoma and pseudo-aneurysm, managed successfully by local compression. The 6 month follow-up data are pending.

Table 1: Angiographic characteristics at baseline and after the procedure

	Baseline	**Post procedure**
Reference Diameter (mm)	2.97 ± 0.58	2.60 ± 0.67
Diameter Stenosis (%)	70.6 ± 14.9	18.3 ± 12.8
MLD (mm)	0.72 ± 0.45	2.12 ± 0.70

DISCUSSION

The RadioCath Trial is a non-randomized, open-label, pilot study to evaluate the safety and performance of a new device for coronary radiation therapy, consisting of a balloon dilatation catheter that can be charged with a solution of sodium [^{186} Re]perrhenate, a predominant beta emitter with a half-life of 3.78 days. The presence of a small portion of gamma rays in the emission of rhenium-186 is an advantage for monitoring the radioactivity during the procedure and detecting a potential leakage of radioactivity outside the device system.

In total, 35 patients with a symptomatic, de novo lesion in a native coronary artery were enrolled in the study. The radiation procedure was started immediately after successful PTCA, defined as a residual stenosis of less than 35%, without severe, flow-limiting recoil or dissection. Most of the patients tolerated the procedure well. In 79% there was only one RTB inflation required to deliver the prescribed dose. Procedural success, without major cardiac complications, was achieved in all 33 patients treated (100%).

With a liquid source there is always a potential risk of leakage of the radioactive solution outside the system with possible contamination of the patient, the operator and the catheterisation laboratory. Since the target lesion is predilated, the RTB is inflated at a low pressure (≤ 5atm.), and the treatment is given prior to stenting, the risk of a rupture of

the RTB is negligible. By frequent monitoring of the radioactivity during the procedure, a leakage outside the patient's body can be detected immediately. The weakest point in the system is the connection of the catheter to the manifold. In one patient, at the end of the procedure, a spill of radioactivity was detected outside the patient's body, due to an accidental tear in the proximal shaft of the RTB catheter, caused by the manipulation of the RTB catheter with metal tongs in stead of plastic clamps. The additional radiation exposure to the patient and the operators was minimal. The further clinical course in this patient was uneventful.

Other disadvantages of this system, compared to other catheter-based beta sources, are the rather complex and time-consuming procedure for charging the RTB catheter, the relatively low energy of the radioisotope, rhenium-186, which prolongs the dwell time. The dose distribution along the RTB covered area is not uniform. Since there is a steep dose decay at the borders of the RTB catheter, 'edge effects' can be induced by additional injury in combination with low-dose radiation at the extremities of the treated vessel segment. Finally, radioactive waste will increase, since the source is only for single use.

On the other hand a 'liquid-filled' balloon device also has its advantages. Compared to other beta sources, dosimetry is less critical, especially in larger arteries, because of the 'auto-centering' of the RTB catheter and the direct contact of the surface of the balloon with the vessel wall. In contrast to solid sources, the dwell time decreases with increasing vessel diameters, and there is no need for an expensive afterloader.

CONCLUSIONS

Coronary radiation therapy is a new, promising technique in the battle against restenosis. In principle, the inhibition of abnormal tissue proliferation into the artery lumen by radiation therapy is an attractive approach. However, many obstacles need to be overcome before CRT will become a generally accepted treatment modality.

Currently, only gamma radiation with iridium-192 has proven to be effective in the treatment of aggressive, recurrent restenosis, in particular diffuse in-stent restenosis (14-20).

The role of beta emitters is less clear. In spite of their safer profile and large investments in their development, the efficacy of beta radiation in the prevention and treatment of restenosis after PCI still needs to be proven.

If beta radiation is effective, based on data from randomized placebo-controlled clinical trials, the indications for beta radiation and the 'ideal' system need to be determined.

We performed a pilot study with a new device, consisting of a balloon catheter that can be charged with rhenium-186, a liquid beta source. Coronary radiation therapy with this device seems feasible and safe. Clinical and angiographic 6 month follow-up data are pending.

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3

Intracoronary Beta-Irradiation of De Novo Coronary Lesions Using a 186Re Liquid-Filled Balloon System

Six-Month Results From a Clinical Feasibility Study

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ABSTRACT

Background

Vascular brachytherapy has shown to be effective for in-stent restenosis, but efficacy in de novo lesions remains uncertain. We evaluated feasibility and outcome of intracoronary beta-radiation therapy in de novo coronary lesions using a ^{186}Re liquid-filled balloon system.

Methods and Results

Thirty-three patients received 20 Gy ^{186}Re beta-irradiation, immediately after balloon angioplasty. The 6-month restenosis rate was 41% (12/29) and restenosis was located within the target lesion in 8 patients and at the edges of the injured and irradiated segment, outside the target lesion, in 4 patients. At 6 months 4 patients (12%), all stented during the initial procedure, had experienced a late (> 30 days) total occlusion.

Conclusions

Intracoronary beta-radiation therapy of de novo coronary lesions using ^{186}Re is technically feasible. No reduction in restenosis was observed. The high incidence of late total occlusions may have been prevented by avoiding new stent implantation and prolonging double antiplatelet therapy.

INTRODUCTION

Restenosis remains a major limitation of percutaneous coronary interventions (1). Even after successful coronary stent implantation, in-stent restenosis due to excessive neointima formation occurs in 7% to 37% of patients (2-6).

Intracoronary ionizing radiation therapy using catheter-based gamma- and beta-emitters has demonstrated a reduction in neointima formation in the porcine coronary restenosis model (7-10). Clinical studies in human subjects have confirmed the feasibility of the technique and have shown a reduction in the rate of recurrent restenosis, particularly in patients with in-stent restenosis (11-17). Recently, a reduction in restenosis has been reported with beta-radiation therapy following balloon angioplasty or stenting of de novo coronary lesions (18-19).

Irradiation of coronary arteries, however, has also revealed new problems, which include: an increased restenosis rate at the borders of the irradiated and injured segment particularly with beta-particle emitting stents, often referred to as edge stenosis; and an increased rate of late (> 30 days after procedure) thrombotic coronary occlusions, particularly when combined with new stent implantation (20-26).

The present study reports clinical and angiographic follow-up results of intracoronary beta-radiation therapy using a rhenium-186 (^{186}Re) liquid-filled balloon device (RadioCath™) in patients treated for a symptomatic de novo coronary lesion.

METHODS

The Radiation Treatment Balloon Catheter Device (RadioCath™)

The RadioCath™ device (Mallinckrodt Inc., St. Louis, Missouri) consists of three components: (1) a 25mm radiation treatment balloon (RTB) catheter; (2) a manifold, containing a shielded vial with a clear colourless solution of sodium [^{186}Re]-perrhenate; and (3) an inflation device (Figure 1).

Liquid ^{186}Re is predominantly a beta-emitter (92.2%). The maximum energy of the beta-particles is 1.077 MeV. It also has limited gamma-ray emissions, the most abundant (9.5%) being an energy of 137 keV. The isotope half-life is 3.78 days. The depth dose profile of a 24mm-long balloon containing 20 mCi ^{186}Re for a 10 minutes exposure is shown in Figure 2. In vitro dosimetry experiments have demonstrated that the dose delivered at 0.5 mm and at 1 mm into the tissue is respectively 44% and 19% of the dose at the surface of the ^{186}Re balloon (27, 28).

Irradiation Procedure

All patients were treated with aspirin (≥100 mg/d) and received heparin (10,000 U bolus) prior to the intervention in order to achieve an activated clotting time > 250 seconds. Aspirin (≥100 mg/d) was continued throughout the study and patients who received stents were additionally treated with ticlopidine (250 mg BID) for one month post procedure.

Immediately following percutaneous coronary angioplasty (PTCA), if the residual stenosis ≤ 35% without flow-limiting dissection, the RTB catheter was positioned across the target lesion. All air was withdrawn from the RTB catheter by creating a vacuum for thirty seconds. The RTB was then charged with the ^{186}Re solution (250 mCi/ml) by inflating the balloon at a pressure of 5 atmospheres. Dwell times to deliver 20 Gy at 0.5 mm into the vessel wall ranged from about 5 to 10 minutes, depending on the size of the artery and isotope activity. The RTB was shielded with a mobile plastic shield outside the patient. This absorbed nearly all beta-particles. A valve system inside the manifold prevented leakage of radioactivity into the inflation device.

During the procedure radioactivity was regularly measured at the patient's chest. Blood samples were taken before and after the procedure to measure any isotope present in the circulation. A 4-inch NaI (Tl) scintillation detector coupled to a multi-channel analyser (Wallac, Turku, Finland) was used for this purpose, which could detect even minute quantities of radioactivity leaked into the patient. After treatment, the RTB catheter was removed by the use of plastic clamps and the device was put into a lead container until radioactive decay. Figures 4 and 5 illustrate the angiographic findings in two patients.

Study Design

The study had a prospective, observational design and was conducted in two tertiary referring centers in Europe. The study protocol was approved by the Institutional Review Boards and the local radiation safety committees of both centers and by the radiation authorities of Belgium and the Netherlands. Written informed consent was obtained from each patient before enrollment. The primary objective was validation of the performance of the RadioCath™ device. Prevention of restenosis was a secondary objective.

Patients were eligible if they were scheduled to undergo standard PTCA of a single symptomatic *de novo* lesion in a native coronary artery. Additional inclusion criteria were a target lesion length ≤ 15 mm and a reference vessel diameter between 2.5 and 4.0 mm. Exclusion criteria were severe recoil or dissection after angioplasty requiring immediate stent implantation; myocardial infarction within 72 hrs prior to PTCA; diffuse disease distal to the target lesion; a bifurcated lesion; and a left ventricular ejection fraction < 30%.

When indicated, stenting was performed after the radiation treatment to avoid shielding by the stent struts and possible damage to the RTB catheter.

Coronary Angiography and Intravascular Ultrasound

Quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) were done at baseline, post-procedure and 6-month follow-up.

In each patient coronary angiograms were recorded in the same projections and after intracoronary administration of nitrates. The inflated and deflated angioplasty balloon and RTB catheter were recorded after every repositioning. QCA was done using the Cardiovascular Measurement System (CMS, MEDIS, The Netherlands) at the Angiographic Core Laboratory of the Brigham and Women's Hospital, Boston, MA (29, 30). At each time point lesion morphology was assessed and reference vessel diameter, minimal lumen diameter (MLD) and percent diameter stenosis were measured. The acute gain was calculated as MLD post-procedure – MLD baseline, and the late lumen loss as MLD post-procedure – MLD follow-up. The late loss index was calculated as late loss/acute gain. A qualitative revision of all angiograms was performed at the angiographic

core laboratory of the University Hospital Gasthuisberg, Leuven, Belgium to detect geographic miss and to evaluate the localization of the restenosis (within the target lesion or at the edges).

All IVUS studies were performed after intracoronary administration of nitrates using a mechanical IVUS system (ClearView, CVIS) with a sheath-based 30-MHz catheter. The IVUS transducer was withdrawn through the stationary imaging sheath at a fixed pullback speed of 0.5 mm/sec. IVUS analysis was performed using planar quantitative analysis at the Core Ultrasound Laboratory of the Washington Hospital Center, Washington DC (31, 32). Lumen cross sectional area (CSA) was measured at the target lesion site with the smallest lumen diameter and at the reference site, defined as the most normal looking vessel cross-section within 10 mm proximal and distal of the target lesion, but before a major side branch. The reference lumen CSA was defined as the average of the proximal and distal reference lumen CSA. Additionally, the external elastic membrane (EEM) CSA was measured at the target lesion site. In case of stenting, the stent CSA, defined as the area circumscribed by the stent struts at the smallest section of the stent, was measured. The plaque + media CSA was calculated as EEM CSA minus lesion lumen CSA as well as the percent area stenosis defined as (reference lumen CSA – lesion lumen CSA) / reference lumen CSA x 100. Changes from post-procedure to follow-up in lesion lumen CSA, EEM CSA, plaque+media CSA and stent CSA were calculated and expressed as percentage of the post-procedure value.

Statistical Analysis

Continuous variables are presented as means ± 1SD and categorical variables as numbers and percentages. Statistical comparison was performed by a 2-tailed paired or unpaired Student's *t*-test or a χ^2 test, when appropriate. A value of $P<0.05$ was considered statistical significant.

RESULTS

Clinical and Procedural Data

From November 1998 to March 1999, 35 patients were enrolled in the trial. Baseline characteristics of all patients are summarized in table 1. Thirty-three patients (94%) received ^{186}Re-radiation therapy and were considered the study population for analysis of the clinical endpoints. Two patients were not irradiated and were excluded for the following reasons: one because of a severe, occlusive dissection after angioplasty requiring immediate stent implantation; and the other because of a technical failure of the inflation pressure monitoring system necessitating termination of the procedure before the RTB was adequately charged.

Table 1. Baseline characteristics

Number of patients enrolled	35
Number of patients treated	33 (94)
Gender	
Male	19 (54)
Female	14 (40)
Age (years)	63 (9)
Risk factors	
Familial predisposition	15 (43)
Hypertension	20 (57)
Hypercholesterolemia	21 (60)
Smoking	22 (63)
Diabetes	7 (20)
Prior myocardial infarction	16 (46)
CCS angina class	
0	2 (6)
I	1 (3)
II	6 (17)
III	14 (40)
IV	12 (34)

Data are presented as n (%) for categorical variables and mean (1 SD) for continuous numbers.

Lesions were located in the left anterior descending artery (n=9), the left circumflex artery (n=11) and the right coronary artery (n=13). The average lesion length was 10.7 ± 5.4

mm (range 4.0 – 28.1 mm) with lesion length exceeding 15mm in 3 patients. Lesion complexity grades according to the modified AHA/ACC criteria were: type A (n=12), type B1 (n=11), type B2 (n=4), type C (n=6). Five patients (15%) had an occlusion of the target vessel at baseline. Stents were implanted after the radiation treatment in 23 patients (70%). The mean acute gain was 1.69 ± 0.67 mm.

Irradiation treatment was administered using 2.5 mm (n=1), 3.0 mm (n=25), 3.5 mm (n=6) and 4.0 mm (n=1) diameter RTB catheters. The mean ratio of the RTB diameter to reference vessel diameter was 1.13. The average dwell time was 6 minutes 58 seconds (range 5 minutes 49 seconds – 9 minutes 58 seconds). Administration of the prescribed dose required in 26 patients (79%) one, in 5 patients (15%) two and in 2 patients (6%) three fractions, respectively, during which the RTB catheter remained intracoronary across the target lesion. During irradiation, the average dose rate over the patient's chest and over the plastic shield was 0.037 mSv/hr and 0.253 mSv/hr, respectively. From the readings of the finger TL dosimeters a maximum procedural exposure of 1.3 mSv for the operator and 0.8 mSv for the cath-lab personnel was calculated.

While no internal leakage of radioactivity occurred, in one patient a minor external spill of radioactivity was detected at the end of the procedure. A detailed examination revealed a small tear in the proximal part of the RTB catheter shaft, outside the patient. Radiation exposure to the patient and the operators was negligible. In-hospital and follow-up course of this patient was uneventful.

Follow-up Data

There were no major cardiac events during hospital stay. Five patients (15%) suffered minor complications: three patients had a slight, post-procedural rise in creatine kinase to 287 U/l (1.5 times upper normal limit), and two other patients each experienced a groin haematoma with pseudo-aneurysm at the instrumented site, which was successfully managed by local compression.

At 6-months 11 patients (33%) had experienced recurrence of angina (CCS grade I (n=1), II (n=1), III (n=4) and IV (n=5)). Of these, three patients had presented with an acute coronary syndrome respectively at 36, 90 and 103 days after the index procedure. An

acute late (> 30 days after the procedure) thrombosis of the target lesion was confirmed by angiography and successfully treated by repeat PTCA in two of the three patients. The third patient did not undergo a repeat coronary angiogram but was successfully treated with thrombolytic therapy. The 6-month follow-up angiogram in this patient revealed no restenosis. All three patients received a new stent during the radiation procedure and none of them were taking ticlopidine at the time of the event. Additionally, a 'silent' total occlusion of the target lesion was present at 6-months in two patients, both stented. The overall 6-month incidence of angiographycally confirmed late total occlusion (LTO) was 12% (4/33) (22).

Six-month follow-up angiography was performed in 29 patients (88%) at 174±25 days on average. One asymptomatic patient refused follow-up angiography. Angiographic data are summarized in table 2. Target lesion restenosis rate (> 50% diameter stenosis) at 6-month follow-up was 28% (8/29). Additionally, restenosis at the proximal or distal edges of the injured and irradiated segment but outside the target lesion was observed in 4 patients (14 %). Overall restenosis rate, including target lesion and adjacent segments, at 6-months was 41% (12/29). Target vessel revascularization was performed in 14 patients (42%) and 7 patients (21 %) were treated for non-target vessel disease progression. Mean lumen late loss was 0.83 ± 0.55 mm and mean late loss index was 0.53 ± 0.38. As expected, acute gain was greater in stented patients, compared to patients treated with balloon angioplasty (BA) alone (1.87 ± 0.64 vs. 1.30 ± 0.57 mm, P=0.03). However, late loss was also greater in stented patients (0.95 ± 0.60 vs. 0.56 ± 0.27 mm, P = 0.07). Restenosis at 6-months was similar in both groups (BA: 33% vs. stent: 45%, P=0.56). While no edge (re)stenosis occurred in the BA group, edge (re)stenosis was observed in 4 patients in the stent group (P=0.15 vs. BA group). Geographic miss, defined as incomplete coverage of the injured segment by the radiation source, occurred in 39% of patients (13/33) (26). No difference in angiographic outcome was seen between patients with and patients without geographic miss.

Table 2. Angiographic data

	Baseline	Post-procedure	Follow-up
Reference Diameter (mm)	2.72 ± 0.50	2.79 ± 0.54	2.71 ± 0.52*
MLD (mm)	0.65 ± 0.40	2.34 ± 0.63	1.51 ± 0.82*
Diameter Stenosis (%)	76 ± 15	17 ± 12	45 ± 25*

Values are means ± 1 SD. * P<0.05 vs. post-procedure (paired Student's t-test).

As shown in table 3, a significant 31% decrease in lumen CSA was observed at follow-up, despite a slight (11%) increase in EEM CSA. Since there was a 48% increase in plaque + media CSA at follow-up, this finding is most likely explained by neointima hyperplasia that is only partial compensated by positive remodelling. Interestingly, a 72% increase plaque + media CSA was observed in stented patients, indicating significantly more tissue growth in stented patients compared to BA patients in whom plaque + media CSA decreased by 5% at follow-up (P=0.04). Moreover a 14% increase in stent CSA was observed at follow-up (P=0.04, compared to post-procedure). A similar observations has previously been reported by de Jaegere et al.(33).

Table 3. Intravascular ultrasound data

	Baseline	Post-procedure	Follow-up
Lesion Lumen area (mm^2)	1.87 ± 0.60	6.31 ± 2.74	4.74 ± 3.00*
EEM area (mm^2)	12.14 ± 4.69	13.21 ± 4.87	15.72 ± 5.60
Stent area (mm^2)		7.14 ± 2.49	8.23 ± 3.23*
Plaque + media area (mm^2)	10.26 ± 4.36	6.98 ± 3.28	10.98 ± 3.98*
Area stenosis (%)	72 ± 9	10 ± 32	36 ± 24*

Values are means ± 1SD. EEM, external elastic membrane. * P<0.05 vs. post-procedure (paired Student's t-test).

DISCUSSION

Intracoronary gamma- and beta- radiation therapy have been proposed to treat restenosis following percutaneous coronary interventions (12-19). Liquid beta-emitting isotopes have several potential advantages compared to solid beta-sources, making liquid-filled balloon devices an attractive approach for delivering ionizing irradiation to the vessel

wall. Radiation treatment can be administered using standard PTCA equipment. Since centering occurs automatically after RTB inflation, complete source contact with the vessel wall is guaranteed, independent from bending of the coronary artery, cardiac motion and lesion morphology. Therefore radial dosimetry is less critical with liquid-filled balloon devices. There is no prolongation of the dwell time in larger arteries and no need for an afterloading device.

The rationale for a dose of 20 Gy at 0.5mm tissue depth in this trial was based on a dose-response study using a balloon-injured porcine coronary artery model (34). Compared to control, a significant reduction in neointima formation in pig coronary arteries was observed with 20 Gy at 0.5 mm tissue but not with 15 Gy (34).

Despite differences in lesion characteristics and radiation dose, the results of our study are similar to a recently published feasibility study with a ^{188}Re liquid-filled balloon device (20). Target lesion restenosis was less with ^{188}Re (12% vs. 28% with ^{186}Re), which can be explained by the higher energy and better depth dose profile of ^{188}Re. The overall restenosis rate, however, was similar in both studies (46% with ^{188}Re and 41% with ^{186}Re) and comparable to the 46% restenosis rate in the control group of the Lovastatin Restenosis Trial, used as an historical control group in our study (35).

The combination of injury and low-dose beta-radiation can exacerbate neointima formation (23 - 26). Edge (re)stenoses (14%) and the high incidence of geographic miss (39%) observed in this study can be explained by the short and fixed source length of the RadioCath™ device. Since there is a sharp decrease in radiation dose at the ends of the RTB catheter, the actual length of the vessel segment that receives the prescribed adventitial dose of 20 Gy is approximately 20 mm, which is identical to the interventional length when using a 20 mm standard PTCA balloon (Figure 2). Additionally, a dose prescription at 0.5 mm into the vessel wall may be insufficient to target the adventitia of severely diseased human coronary arteries. Perfect matching of RTB diameter to the vessel size is critical with this device. Additional injury by the RTB catheter can occur, even at low inflation pressures, especially when the RTB diameter exceeds the vessel diameter. The mean ratio of RTB to artery diameter was 1.13 in this study and could have contributed to the edge restenoses.

The delay in the healing response within irradiated arteries may promote thrombosis (36). Late total occlusion (LTO), confirmed by angiography, occurred in 4 patients (12%) in this trial, each received a new stent at the time of radiation treatment. Two of the 4 patients with LTO presented with an acute coronary syndrome, two other patients had a silent occlusion of the target lesion, confirmed by the 6-months angiogram. Another stented patient experienced an acute myocardial infarction 90 days after the procedure, most likely due to late thrombosis, although no angiogram was performed. Delayed re-endothelialization of the stent surface has been suggested as a potential mechanism of this severe, life-threatening complication (21, 22). Compared to other beta-emitters, such as ^{188}Re or ^{32}P, the maximum beta-energy of ^{186}Re is relatively low (1.077 MeV) and its beta-rays are less penetrating. Therefore, the dose at the luminal surface will be higher with ^{186}Re for a similar adventitial dose compared to other beta-emitters. This may increase the risk for late thrombosis. At the time of this study, standard antiplatelet therapy for stented patients consisted of continuous aspirin along with ticlopidine for 1 month. None of the patients with late thrombosis were taking ticlopidine at the time of the event. It is unknown whether extending the double antiplatelet therapy for a longer period would have prevented these events.

Finally, a liquid source always involves a potential risk of radiation leakage outside the system with possible contamination of the patient, the operator and the catheterization laboratory. While no internal leakage of radioactivity occurred in this study, in one patient a minor external spill of radioactivity was detected due to a tear in the RTB catheter shaft.

Limitations

This study was a feasibility study in a small patient population and without a randomized, controlled design. Therefore efficacy data should be interpreted with caution.

CONCLUSIONS

Intracoronary beta-radiation therapy using a ^{186}Re liquid-filled balloon catheter is technically feasible. No significant effect was observed with respect to the overall restenosis

rate. Edge (re)stenosis may be avoided by increasing the length of the irradiation source and by carefully matching the RTB diameter to vessel size. The high incidence of late total occlusions warrants a prolonged double antiplatelet therapy, particularly in patients who received a new stent at the time of radiation treatment. Moreover, intracoronary radiation therapy should be avoided in patients with de novo lesions treated with stent implantation.

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4

Beta-radiation Reduced the Reactivity of Extra Cellular Matrix Proteins, Resulting in Decreased Platelet Adhesion

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ABSTRACT

Background

Thrombus propagation on disrupted plaque is a major cause of acute coronary events and serious complication after coronary intervention. Beta-radiation treatment may alter the reactivity of certain vessel wall extracellular matrix proteins, in particular vWF and collagen and radical-mediated prevention of intimal hyperplasia after coronary intervention. In this study we examine how beta-radiation affects ECM protein thrombogenicity.

Design and Methods

ECM protein thrombogenicity was quantified by platelet coverage evaluation, aggregation-analysis and real-time recording, measuring the binding of domain-specific antibodies to treated surface and Fourier transform infrared spectroscopy (FTIR) before and after beta-radiation treatement.

Results

Beta-radiation significantly decreased platelet adhesion to vWF and collagen type III. The platelet coverage evaluation and aggregation-analysis showed smaller thrombi present on beta-radiation treated collagen, the very first step of platelet adhesion, the first touch down of a platelet on the surface was greatly diminished. The distance over which the platelets roll over collagen to reach a full stop was increased. Measuring the binding of domain-specific antibodies to treated surface show beta-radiation treatment affected the A1, A2 and A3 domains, but not the D'-D3 and B-C1 domains. Studying in collagen secondary structure and the surface properties by Fourier transform infrared spectroscopy (FTIR) show huge structural alterations after beta-radiation.

Conclusions

Beta-radiation treatment decreases the thrombogenicity of vessel wall extracellular matrix proteins, in particular vWF and collagen, resulting in decreased platelet adhesion and aggregation. The vessel wall become lowly prone to thrombosis and might help reduce the onset of acute coronary events and of acute coronary occlusion after intravascular interventions. The results would provide the fundamental understanding of the protein denature under Beta-radiation at the molecular level.

INTRODUCTION

Intravascular Brachytherapy (IVBT) has been used as a tool to reduce restenosis after Percutaneous Coronary Intervention (PCI). In several clinical trials results were shown to be favourable when compared to placebo.1-6 Single doses in excess of 7–56 Gy intracoronary catheter-based beta-radiation have clearly shown a reduction in neointima formation and reduced vessel remodelling in several animal models and clinical trials.7,8 Intracoronary catheter-based beta-radiation is thought to produce reactive oxygen specimens and/or oxygen radicals that alter vascular wall biology and vessel wall protein function. One of the first steps occurring after vascular injury is the adherence of platelets to the subendothelium and the exposed media.9,10 This is a complex mechanism that involves several steps11,12. Briefly, after denudation of endothelial cells, there is exposure of the extracellular matrix (ECM), of which the major adhesive proteins are fibrinogen, von Willebrand factor (vWF) and the fibrillar collagen types I and Ill.13,14 Platelets can bind directly to fibrinogen and vWF already present in the ECM. The role of collagen is more complex, as collagens are not only important adhesive proteins but also potent platelet agonists leading to platelet aggregation.[15] Platelet adhesion to collagen can occur directly by interaction of collagen with platelet membrane proteins, of which glycoproteins GPVI and the integrin GPIaIIa are the most important ones.[16] Platelet adhesion to collagen at high shear rates occurs indirectly via binding circulating vWF to collagen, creating a bridge between both the platelet GP-Ib receptor and collagen. This process activates the platelets and causes a conformational change, exposing the GP-IIb/IIIa receptor on the platelet membrane. The GP-IIb/IIIa receptor, in turn, binds to adhesive proteins such as fibrinogen and vWF to form a bridge between platelets, thus causing platelet aggregation.

Beta-radiation with an intracoronary centred balloon catheter and automated delivery unit also may alter the ECM like radical-mediated prevention of intimal hyperplasia by photodynamic therapy.[17] In this study we examine how beta-radiation affects ECM, vWF, fibrinogen and collagen thrombogenicity by measuring platelet adhesion with single pass flow and real time recording system. Considering the multifactorial roles of vWF and

collagen in mediating platelet adhesion, further studies were carried out to examine how beta-radiation affects these specific proteins by domain-specific antibodies.[18]

Because of no enough domain-specific antibodies for collagen, we try use Fourier transform infrared spectroscopy (FTIR) which as a powerful analytical technique, has been successfully used to probe the molecular environments and the structural changes of the active centers of proteins at the molecular level [19-21] to study of the influence of the Beta-radiation on the secondary structure, the external morphologies and the surface properties of the collagen by using. Gaber has investigated the effect of gamma-radiation on the molecular properties of bovine serum albumin (BSA) with FTIR. They found that radiation changed the secondary and tertiary structures, molecular weight and optical anisotropy of BSA[22]. In addition, FTIR has been used to monitor structural changes of redox-induction proteins labeled with an isotope or adsorbed on different modified surfaces[23-24], the change of the secondary structures on substrates modified with biomedical polyurethanes and perfluorinated polymer[25], and conformational assessment of protein adsorbed on biocompatible materials[26].

DESIGN AND METHODS

Coating of coverslips

Plasma vWF was purified from human cryoprecipitate, using a Bio-Gel A-15m (BioRad) column as described[27,28] and stored at -20°C. Coverslips were cleaned overnight in a chromium trioxide solution, rinsed with distilled water and coated by incubating each coverslip with 100 µL of purified vWF in PBS (10 µg/ml) for 1 h, followed by incubation in 1% human albumin (HA). For fibrinogen and collagen type III coating, coverslips were cleaned with ethanol, rinsed and air-dried. Coverslips were incubated with 100 µg/ml fibrinogen (Enzyme Research Labs, South Bend, IN) for 1 h, followed by incubation in 1% HA. Human placenta collagen type III (Sigma Chemical Co., St. Louis, MO) was solubilized in 50 mM acetic acid and sprayed at a density of 30 µg/cm^2 with a retouching airbrush Badger model 100, Badger Brush Co., Franklin Park, IL). After the spraying

procedure, the coverslips were incubated for 1 h with 1% HA in PBS (10 mM phosphate buffer, pH 7.4; 0.15*M* NaCl). All coated coverslips wore stored in PBS at 4°C before perfusion experiments were performed.

Beta-radiation application for the coverslips

Intracoronary catheter-based beta-radiation is performed with an intracoronary centred balloon catheter and automated delivery unit [Galileo® intravascular radiotherapy system (IRS), Guidant, Houston TX 77054, USA]. The device has been described in detail elsewhere.[29] In summary, it consists of four components: 1, the source delivery unit; 2, the centering catheter, 3, the beta-radiation source wire and 4, the inactive wire. The longitudinal distance of the 'full' prescribed dose (100% isodose) coverage, measured by radiochromic films, is about 22mm [30,29] constituting the effective radiation length. To mimicking this operation, we use Beta-^{90}Sr irradiation treatment of coverslips coated with vWF, collagen type III, fibronectin, and fibrinogen without an intracoronary centred balloon catheter. Boron-doped p-type single crystal silicon (100) wafers with a resistivity in the range 1-15 cm were cleaved into 1cm pieces. Before each experiment, the silicon pieces were degreased by sonication in acetone and ethanol, and then rinsed with deionized water. The cleaned silicon pieces were then placed horizontally on home-made sample shelves schematically shown in figure 1. A portion of collagen solution was dropped onto the silicon surface. Generally, isotope 90Sr disintegrates to 90Y, releasing beta-radiation. The radiation dose can be calculated according to equation (b2). [31].

$$^{90}Sr \rightarrow {}^{90}Y + \beta^{-1} \quad (1)$$

$$P(^{90}Sr - {}^{90}Y) = \frac{A \times 1770 \times \overline{E}(^{90}Y)}{s \times \overline{E}(^{32}P)} \quad (2)$$

where P is the radiant quantity and A is the degree of activity for the radioactivity of an isotope; denotes the energy and s is the surface area of ^{90}Sr. According to equation (2), A radiation time of 13 s corresponds to a radiation dose of 10 Gy, for example. Within the same distance of Beta-^{90}Sr radiation, at defined different radiation time the protein solution on the silicon surface was taken for structural and morphologic analysis.

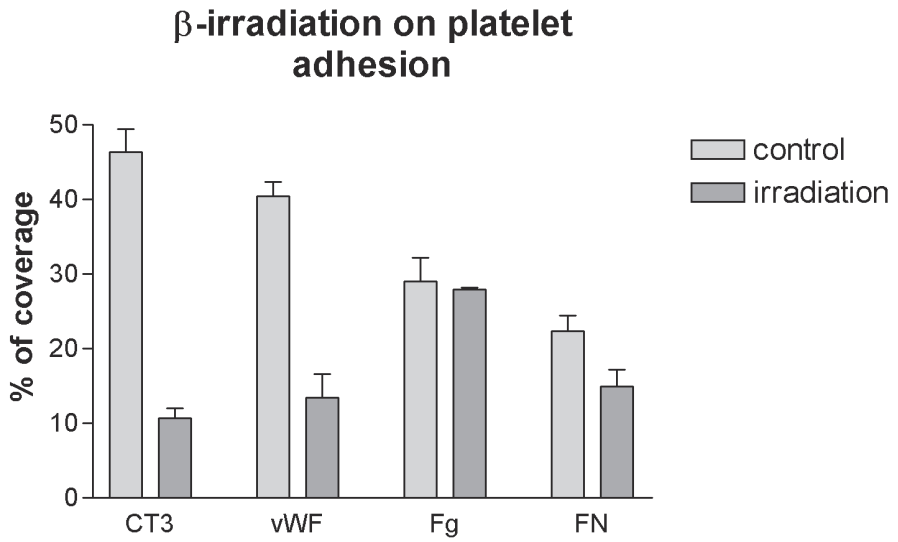

Figure 1. Platelet adhesion to vWF and collagen-III. One group was BRT treated (irradiation). BRT-treated and control coverslips were perfused in single pass perfusion chamber, using a shear rate of 300 s^{-1} (Fg, Fn) 1000 s^{-1} (vWF) or 1600^{-1} (CT3) for 5 min. BRT caused a significant reduction of platelet adhesion to vWF and collagen-III. Values are mean ± standard error of the mean.

Platelet Perfusion studies

After Beta-radiation treatment, the coverslips were blocked again by 1% HA. Blood used for platelet studies was collected from healthy donors receiving no medication. For vWF and fibrinogen perfusions, blood was anticoagulated 1:10 vol/vol with 110 mM trisodium citrate (pH 7.4) and kept at room temperature. For collagen perfusions, blood was anticoagulated with 1: 10 vol/vol 200 U/ml low molecular weight heparin (Fragmin, Kabi Pharmacia, Stockholm, Sweden) in 0.15 *M* NaCl. Temperature of whole blood was raised to 37°C and recirculated for 5 min through a specially devised vacuum perfusion chamber with well-defined rheologic characteristics, as we previously described[32,33,14]. Perfusions were performed at their optimal shear rate of 300 s^{-1} (fibrinogen, fibronectin), 1000 s^{-1} (vWF) and 1600 s^{-1} (collagen).[34-37, 28]

Evaluation of platelet adhesion coverage

Both coverslips were perfused in sequence in a random order, thus exposing the control and beta-radiation coverslips to the same blood conditions. After perfusion, the coverslips were removed and rinsed in 10 mmol/l N-2-hydroxy-ethylpiperazine-N'-2-ethanesufonic acid buffer (HEPES, pH 7.35) containing 150 mmol/l NaCl, fixed in 0.5% glutaraldehyde, dehydrated in methanol and stained with May-Grunwald-Giemsa. Platelet adhesion to the coverslip was measured with light microscopy coupled to an image analyzer system using the Optimas 6.0 software (DVS, Breda, the Netherlands). Thirty randomly selected coverslip areas were evaluated, and the results from triplicate coverslips were averaged. Platelet adhesion was expressed as the percentage of the surface covered with platelets.

Aggregation size analysis by using the Watershed program

Only adhesive collagen type III induced aggregate-formation under 1600/s flow conditions. The aggregation size was evaluated, using the Watershed program provided by the Optima software package, version, 6.51.199, Optimas Corporation, Bothell, Washington 98011, USA.[30,33] The Watershed technique separates confluent or overlapping objects on the basis of colour intensity levels. This technique was reproducible with a variation coefficient of 9.8%. The algorithm gets its name from the concept behind its implementation. The starting point of the watershed is an image in which there are dark valleys or "wells". The watershed program finds the lowest point (local minimum) in each well and fills each of these wells with a starting "water level". The starting water level causes shallow wells to join together to form small lakes. These lakes represent the seed points of the objects to be separated. When the watershed is completed, there will be an object for each lake. To each lake, the watershed begins filling (adding intensities) examining pixels in the neighbourhood to make sure none of the lakes touch one another. As the lakes fill they become larger and there is a tendency for them to join. If two lakes are about to join, the watershed builds a dam between them so they remain separated.

Platelet aggregation size on collagen type III surface was subdivided in % of surface covered with (1) contact and spread platelet with an area of < 8 μm^2, (2) aggregated with an area between 8-40 μm^2, (3) aggregated with an area between 40-200 μm^2, (4)

aggregated with an area between 200-400 μm^2, (5) aggregated with an area between 400-600 μm^2, (6) aggregated with an area >600 μm^2,

Real time flow recording[32]

Whole blood was labelled by mepacrine (Sigma, St. Louis, MO, USA, final concentration of 10μM), warmed to 37°C, aspirated through a real time view perfusion chamber with a syringe pump (Harvard Apparatus, South Natic, Ma, USA). A single passage parallel plate vacuum chamber perfusion chamber (vacuum chamber) with leak-proof, reversible sealing of the coverslip and chamber by vacuum force for real time dynamic monitoration in confocal laser scanning microscope was developed. The chamber contained an blood inlet, blood outlet, warm water inlet, warm water outlet and a vacuutn channel connect. On the top of the chamber a silicone rubber gasket was placed. A hole was cut in this silicon sheet to create a perfusion slit, connecting the blood inlet with the blood outlet. On both sides, next to the flow area, two slits was cut in the silicon sheet to obtain vacuum compartments. The coverslip was leak-proof, reversible sealing onto silicone sheet by vacuum force. Blood was preincubated for 5 min with mepacrine. Blood was aspirated through the chamber placed on an inverted fluorescence microscope (DM RXE, Leica, Weitzlar, Germany), which was equipped with a B/W CCD-video-camera (Sanyo, Osaka, Japan), coupled to a Pioneer DVD hard disk recorder (HDR) DVR-5100H. The perfusion shear rate used was the same as that for the other perfusion studies. The perfusion images were recorded with a time interval of 80 msec. The images were automatically evaluated with a Quantimet 570C image-analysis system (Leica/Cambridge LTC, Cambridge, UK) and software.

Recombinant specific vWF domains variants and production of antibodies directed against specific vWF domains

Mature vWF consists of a 2050-residue monomer that contains multiple copies of so-called A, B, C, and D type domains and one CK (cystine knot) domain arranged in the order D1-D2-D'-D3-A1-A2-A3-D4-B-C1-C2-CK. Disulfide bond formation between N-terminal D3 domains and between Cterminal CK domains generates vWF multimers

that consist of up to 80 monomers. The D'-D3 domain contains the binding site for FVIII and heparin. The A1 domain contains the binding site for glycoprotein Ib, heparin and one minor binding site for collagen. The A3 domain (residues 920–1111) contains the major binding site for collagen types I and III. The C domain contains the binding site for GPIIbIIIa. To further delineate how beta-radiation affected the vWF protein, antibodies directed against specific vWF domains were used: Monoclonal Antibody (MoAb) RAG-35 (Generous gift of dr. J.A. van Mourik, Sanquin research, Amsterdam, Netherlands) directed against the A1 domain; RAG-40 (Generous gift of dr. J.A. van Mourik, Sanquin research, Amsterdam, Netherlands) directed against the D4 domain, vWF9 (Generous gift of dr. C.V. Denis, INSERM U143, Le Kremlin-Bicetre, France;), A monoclonal antibody (Mab9) directed against the C1 domain of human vWF, this Mab inhibits interactions between VWF and GPIIbIIIa and between VWF and $\alpha_v\alpha_3$. MoAb RU1 directed against the A2 repeat of human vWF, MoAb RU5 directed against the A3 repeat of human vWF and a polyclonal rabbit antibody directed against the D'-D3 region were prepared in our laboratory (Utrecht). Recombinant A2, A3, D'-D3 of human vWF, was expressed and purified. For production of monoclonal antibody RU1 and RU5 ($IgG_{2a,k}$) hybridoma cells were injected in mice, and ascites fluid was collected (Eurogentec, Seraing, Belgium). IgG was purified on a protein G-Sepharose column, and Fab fragments were generated using an ImmunoPure Fab kit (Pierce, Rockford, IL). RU5-Fab was further purified with A3-affinity chromatography. Polyclonal anti-vWF peroxidase labelled antibody was obtained from Dako (Glostrup, Denmark). The antibody directed against the D'-D3 region was a polyclonal rabbit antibody directed. For staining of MoAb RAG-35, 40, RU-1,5,8, D'-D3, and vWF9 labelling, the secondary antibodies were used, coupled to peroxidase (Dakopatts). Antibody binding to vWF was quantified as follows: coverslips were coated with vWF and blocked with human albumin as described previously, followed by incubation for 1 h with 100 µl of 3% bovine serum albumin and primary antibody to a final concentration of 10 µg/ml. After incubation with the peroxidase-labelled secondary antibody (100 µl, 10 µg/ml) for 1 h, coverslips were rinsed and placed in six-well plates and covered with 2 ml of phenylenediamine (OPD) buffer. Coloring was stopped after 8 min with 400 µl of 3 N H_2S0_4 per well and

subsequently, 150 µl from each well was transferred to wells of a 96-well plate. Optical density was measured at 492 nm. PBS was used as a negative control, and polyclonal anti-vWF Ab was used as a positive control. Results were expressed as percentage of the control.

Fourier transform infrared spectroscopy (FTIR) measurement

FTIR samples were prepared by mixing a collagen solution with or without Beta-^{90}Sr radiation and KBr powder to form transparent KBr pellet. After drying with nitrogen, infrared spectra of the samples were recorded on a Tensor 27 Fourier transform infrared spectrometer (Bruker, Germany) equipped with a liquid-nitrogen-cooled mercury-cadmium-telluride (MCT) detector. Transmission spectra were collected in the wavenumber range of 600 and 2000 cm^{-1}over 64 scans at a resolution of 4 cm^{-1}. The final transmission spectra were calculated as the ratio of R/R_0 of the sample spectrum (R) containing protein to the reference spectrum (R_0) of pure KBr pellet.

Statistical analysis

All perfusions were performed in triplicate for each condition. The results are presented as the mean ± SEM from experiments with blood from 3 different donors, unless indicated otherwise. One-way Analysis of Variance (ANOVA) and Tukey-Kramer Multiple Comparisons Test evaluation included calculation of mean values, standard error of the mean, medians, minimum and maximum values, nonparametric test for comparison of every two groups. All reported P values are two-sided and P values below 0.05 were considered to indicate statistical significance. All analyses were performed with the use of GraphPad, Prism and Instat, software, version 4.00, San Diego, USA.

RESULTS

Beta-radiation treatment significantly decreased platelet adhesion to vWF and collagen type III and had no effect on adhesion to fibrinogen and fibronectin.

To investigate whether beta-radiation is involved in platelet adhesion to immobilized collagen type III or vWF, we perfused reconstituted blood over immobilized beta-radiation treated collagen type III and vWF. In all perfusion experiments, the controls of each group consisted of non- beta-radiation treated coverslips. For each group, we evaluated if beta-radiation treatment influenced the amount of platelet adhesion. Platelet adhesion to HA-coated coverslips was negligible. As shown in Figure 2, beta-radiation treatment significantly decreased platelet adhesion (dark bar) compared to controls (grey bar) for vWF (40.5±1.9% vs 13.4±3.2%; P =0.0184) and collagen type III(46.3±3.0% vs 10.6±1.3%; P =0.0086). Compared to controls (grey bar) beta-radiation had no effect on platelet adhesion (dark bar) to fibrinogen (29.0±3.1% vs 27.9±0.3%; P =0.7658) and fibronectin (22.4±2.0% vs 14.9±2.3%; P =0.1334)(Figure 2). In all experiments, platelet adhesion was homogenous and representative samples were taken from the center of the coverslip.

Morphologically decrease in platelet adhesion coverage on collagen type III was associated with a decrease in platelet aggregate formation. The smaller thrombi present on beta-radiation treated collagen

Only platelet adhesion to collagen type III was with aggregates. Morphological analysis of aggregation size by staining with May-Grunwald-Giemsa and using the Watershed program showed that, bigger thrombi present on control collagen type III surface. 0.8% of total coverage is aggregation, which size is between 8-40 μm^2, 9.7% of total coverage is aggregation, which size is between 40-200 μm^2, 10.4% of total coverage is aggregation, which size is between 200-400 μm^2, 15.4% of total coverage is aggregation, which size is between 400-600 μm^2 and 63.7 % of total coverage is aggregation, which size is between >600 μm^2. The smaller thrombi present on beta-radiation treated collagen. type III surface. 6.2% of total coverage is aggregation, which size is between 8-40 μm^2, 36.1% of

total coverage is aggregation, which size is between 40-200 μm^2, 22.3% of total coverage is aggregation, which size is between 200-400 μm^2, 15.3% of total coverage is aggregation, which size is between 400-600 μm^2 and 19.2 % of total coverage is aggregation, which a size is between >600 μm^2. These results are presented in Figure 3.

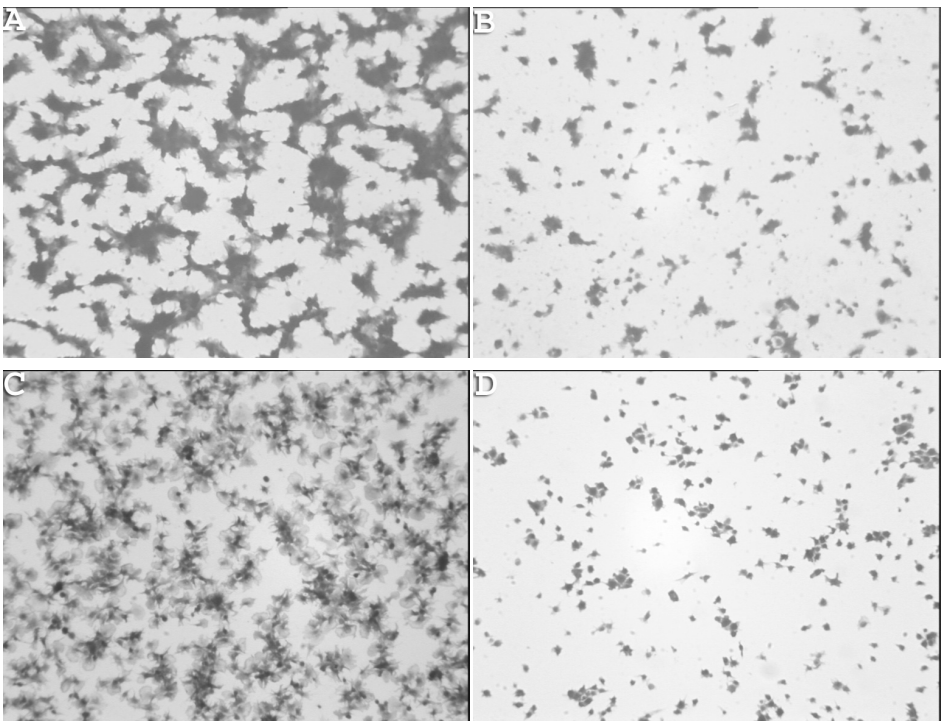

Figure 2. Morphology of platelet adhesion to collagen-III and vWF after perfusion at shear rate 1600/s or 1000/s for 5 min. Coverslips were stained with May-Grunwald-Giemsa. Adhesion to untreated collagen-III (A) was homogenous, with aggregates. Platelet adhesion to BRT treated collagen-III (B) was decreased significantly, with few aggregates. Adhesion to untreated vWF (C) was homogenous, with spreading. Platelet adhesion to BRT treated vWF (D) was decreased significantly, without spreading platelet.

Real time fluorescence labelling platelet adhesion recording and analysis

Only adhesion to vWF and collagen type III was greatly diminished after beta radiation-treatment. The analysis of platelet deposition on beta-radiation treated collagen type III (Figure 3 collagen.avi) showed that the very first step of platelet adhesion, the first touch down of a platelet on the surface was greatly diminished. Also the distance over which the platelets roll over collagen type III to reach a full stop was diminished. This would indicate beta-radiation decreased the reactivity of collagen, resulting in decreased platelet adhesion (to collagen).

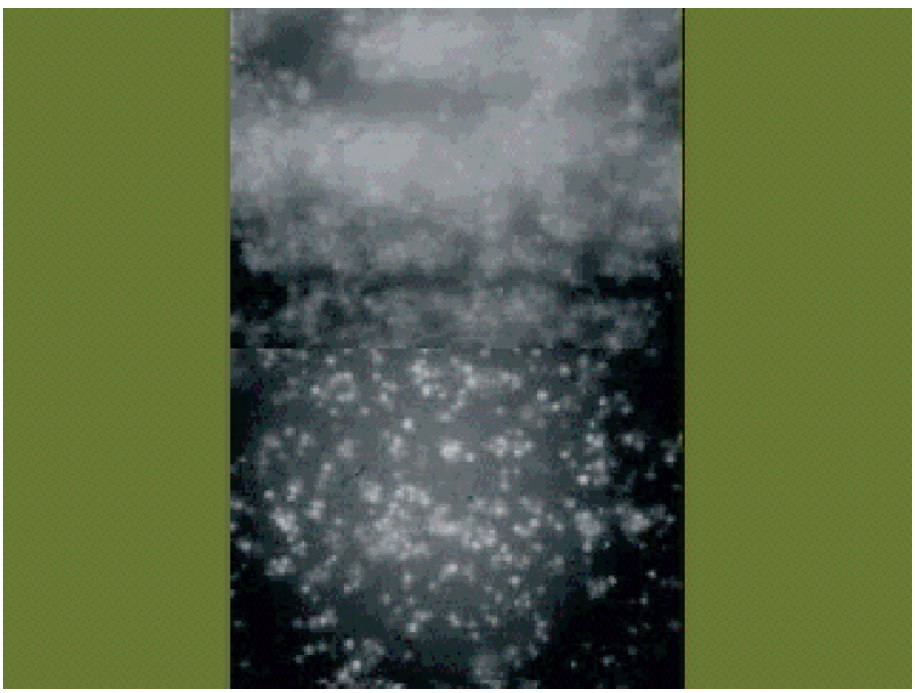

Figure 3. The last image from movie show of Platelet adhesion to collagen Type III, control (upper) and BRT treated (down).

An ELISA study of normal vWF surface and beta radiation-treated vWF surface with domain specific monoclonal antibodies

As platelet adhesion to collagen type III at a shear rate of 1600 s^{-1} was almost completely dependent on vWF, [24] we reasoned that a major damage of beta-radiation was through modification of vWF. To further study this we performed an ELISA on normal vWF surface and beta radiation-treated vWF surface with domain specific monoclonal antibodies (figure 4). The recognition of beta radiation-treated vWF on surface by antibodies recognising domains A1 and A2 on surface was completely lost (22.4% of control and 17.9% of control, respectively), while the antibody recognising domain A3 on surface was partly reduced (66.1% of control). The recognition of beta radiation-treated vWF on surface by antibodies recognising domains D'D3, D4 and B-C1-C2 was same compared with control (82.9% of control, 81.2 of control and 91.7 % of control, respectively) These results showed that beta-radiation affects mostly the AI, A2 and A3 domains of the vWF molecule on surface, whereas the D'-D3 and B-C1 domains on surface remain unaffected. The ligands binding to these domains of vWF on surface have been indicated in the Figure 4 and suggest a significant decrease in binding capacity of the GP-Ib, heparin and collagen ligands to beta radiation-treated vWF on surface.

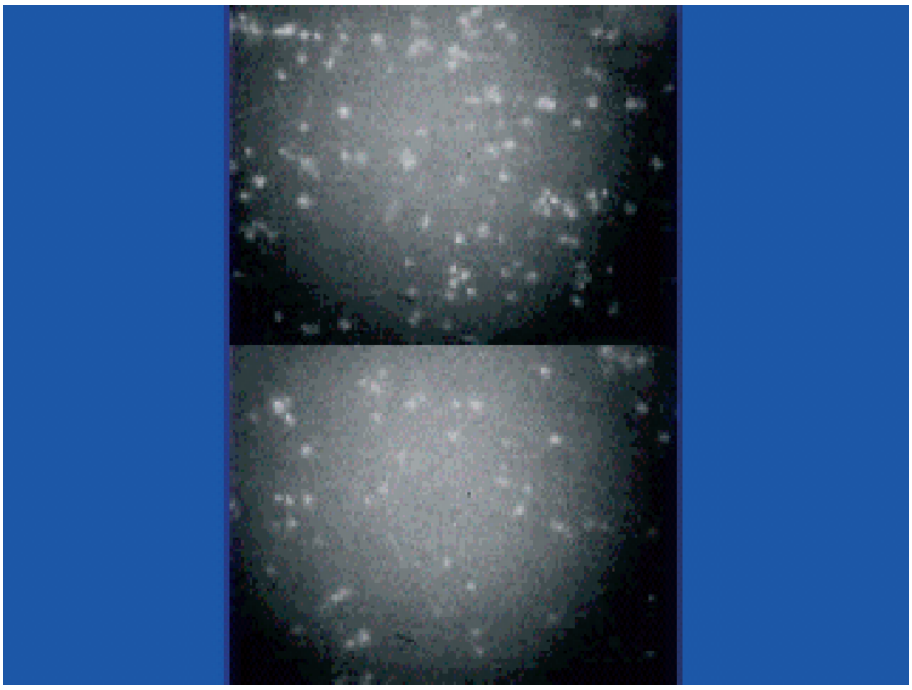

Figure 4. The last image from movie show of Platelet adhesion to to vWF, control (upper) and BRT treated (down).

FTIR spectra of the collagen treated with Beta-radiation dose of 0 Gy (a); 10 Gy (b); 20 Gy (c) and 30 Gy (d)

We studied the structural change of the collagen upon radiation with different doses of Beta-radiation treatments. Figure 5 shows the results of collagen samples radiated with ^{90}Sr at 0 Gy (a), 10 Gy (b) and 20 Gy (c). It is clear that the secondary structure of the protein changes significantly upon Beta-radiation treatments. The spectroscopy of an untreated collagen displays the detailed IR features corresponding to the secondary structure of collagen, indicating that the bioactivity of the protein is retained. The characteristic bands of amide I and amide II should provide detailed information on the secondary structure of the polypeptide chain. The amide I band (at ca. 1601 cm^{-1}) is attributed to the C=O stretching vibration of peptide linkages in the β helix chain or α chain of protein. The amide II band (at ca.1528 cm^{-1}) results from a combination of the N-H bending and

C-N stretching of the amide plane in the backbone of protein. The amide III band at about 1333 $cm^{-1}$is due to the $COOM^{+}$ vibration. The infrared peak located at ca. 1414 cm^{-1}can be attributed to the bending vibrations of $CO\text{-}NH_2$ and C-H in the complicated structures of the polypeptide chain. The intensities of most of the bands decrease with the increase of Beta-radiation dose or even disappear at higher radiation doses.

The new wide peak at about 1105 cm^{-1} is induced by the $C\text{-}NH_2$ vibration, and the peaks at ca. 910 cm^{-1}, 891 cm^{-1} and 696 cm^{-1}can be ascribed to the vibrations of C=C bonds in the side chain of the protein backbone.

In general, after the protein was treated with Beta-radiation at different radiation doses, their infrared spectra changed significantly. Beside the disappearance of the typical FTIR features of the collagen (1602 cm^{-1}, 1510 cm^{-1}, 1404 cm^{-1}, 1333 cm^{-1} and 913 cm^{-1}) upon radiation, some new bands were also observed. At a radiation intensity of 10 Gy, a new peak at ca. 1630 cm-1 attributed to the conjugated vibration of C=C and C=N bonds begin to appear. The intensity of this band increases gradually with the increase of the radiation time. Another significant change is the small sharp band at 1105 cm^{-1}due to the C-NH, vibration, which evolves to a large broad band at 1090 cm-1 when the radiation dose exceeded 20 Gy. These changes of the FTIR features demonstrate that the secondary structures of collagen have been destroyed by the Beta-radiation at 20 Gy.

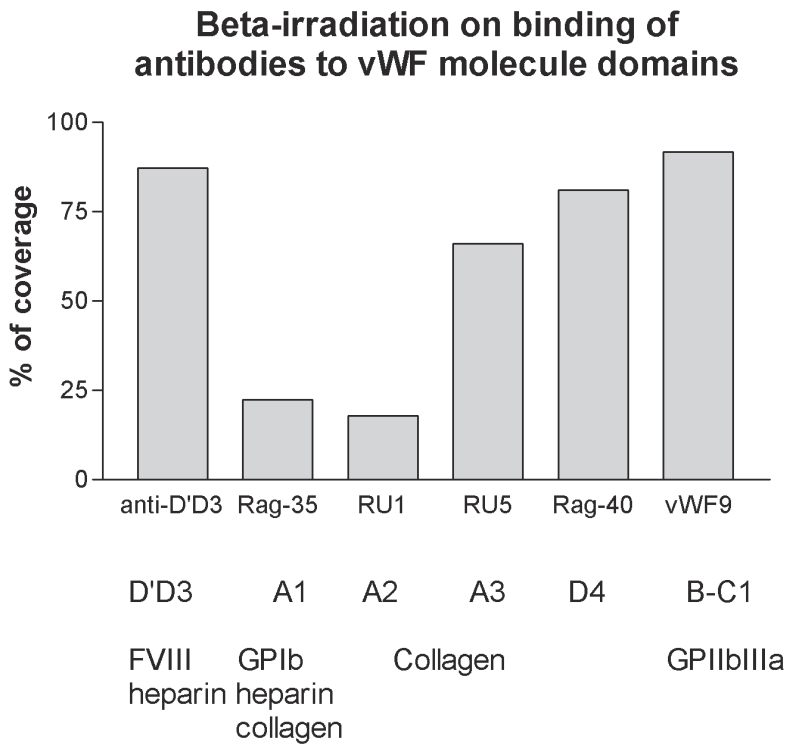

Figure 5. Binding of antibodies directed against different domains of the BRT-treated vWF molecule, expressed as a percentage of the untreated control BRT-treated (n = 6) and control (n = 6) vWF coated coverslips were incubated with monoclonal antibodies directed against specific domains of the vWF molecule. After coloring, the optical density was measured. This figure shows that BRT affects mostly the AI, A2 and A3 domains of the vWF molecule, whereas the D'-D3 and B-C1 domains remain unaffected The ligands binding to these domains have been indicated in the figure and suggest a significant decrease in binding capacity of the GP-Ib, heparin and collagen ligands to BRT-treated vWF.

DISCUSSION

The major source of vWF is plasma. Besides plasma, vWF is present in the alpha granules of platelets and vWF is present in the subendothelium.[28] Injury to the vessel wall results in the loss of endothelial cells, exposure of blood to collagen and vWF for platelet adhesion. It is well known that after intracoronary balloon catheter, there is eradication of the endothelial cell layer and, thus, exposure of the subendothelial collagen and vWF. After the initial step of adhesion, platelets become activated, resulting in platelet-platelet interaction leading to aggregation formation.[11] At higher shear rates, the interaction between vWF in the vessel wall and platelet glycoprotein GPIb is essential to allow platelet adhesion. Before vWF can interact with GPIb, it should first bind to collagens present in the vessel wall.[12] Depending on the nature of the vessel, collagen content ranges from 20% in the aorta wall [35,36] to 40% in the smaller arteries and is even higher in the venous vascular wall.[37] Here we show that after beta-radiation treatment platelet adhesion is severely decreased to collagen type III (23.0%) and vWF (33.1%), but not to fibrinogen and fibronectin. Apparently, vWF and collagen are more sensitive to oxygen radicals than the other two proteins.

Considering the multiple roles of the vWF molecule in platelet adhesion, we investigated how β-beta-radiation affects its different functional domains (Figure 4). The results of these experiments clearly demonstrate that after beta-radiation of vWF, there is impaired antibody-binding capacity to the A-type domains. Apparently, the A domains have lost their proper conformation. Both the A1 domain and the A3 domain contain a disulphide bridge that is important for the stabilisation of their three-dimensional conformation. Although not proven, it is tempting to speculate that these disulphide bridges are oxidized. The recognition of beta radiation-treated vWF on surface by antibodies recognising domains A1 and A2 on surface was completely lost (22.4% of control and 17.9% of control, respectively), while the antibody recognising domain A3 on surface was partly reduced (66.1% of control). The ligands binding to these domains of vWF on surface have been indicated in Figure 4 and suggest a significant decrease in binding capacity of the GP-Ib, heparin and collagen ligands to beta radiation-treated vWF on surface.

The loss of recognition by an antibody that can inhibit the binding of vWF on surface to the platelet receptor GPIb, clearly indicates a reduced binding capacity to the platelet membrane GP-lb receptor. Although the evidence provided is indirect it could explain the reduced platelet adhesion to vWF found after beta-radiation The A3-domain of vWF on surface contains the collagen-binding site and beta-radiation might also results in reduced capacity of vWF to bind to collagen. Of interest was the fact that the B-Cl domain (platelet GP-IIbllIa-binding site) was largely unaffected by beta radiation. As this domain is important in platelet aggregation, one would expect similar aggregate formation on both beta radiation-treated and untreated vWF on surface. This coincides with our observations, where there appears to be less "primary" adhesion (via GP-Ib), but in relation to the lower adhesion we observed similar aggregate formation.

Collagen is built up out of three chains that are intertwined to form a triple helix. The three dimensional structure of collagen is essential for its interaction with platelets. Disturbance of the triple helix results in loss of platelet adhesive and aggregation properties. After collagen was treated with beta-radiation at different radiation doses, their infrared spectra changed significantly. The results are shown in Figure 5 Before Beta-radiation, the IR spectrum (curve a) displays the detailed features corresponding to the second structure of collagen, indicating that the bioactivity of the protein is retained. The characteristic bands of amide I and amide II would provide detailed information on the secondary structure of the polypeptide chain of collagen. The amide I band (at ca. 1602 cm^{-1}) is 80% attributed to the C=O stretching vibration of peptide linkages in the b helix chain or a chain of protein. The amide II band at 1506 cm^{-1} is 60% due to N-H bending and 40% due to C-N stretching of the amide plane in the backbone of protein; this region also contains potential cofactor and side chain vibrations. In addition, the amide III bands at 1333 $cm^{-1}$is due to the $COOM^{+}$ vibration for a-helix, and the band at 1250 $cm^{-1}$is for the random coil peptide chain. The IR peak located at ca. 1405 cm^{-1} can be attributed to the bending vibrations of $CO\text{-}NH_2$ and C-H in the complicated structures of polypeptide chain. The broad peak at about 1125 cm^{-1} is induced by the C-NH2 vibration, and the peaks at ca. 913 cm^{-1} can be ascribed to the vibrations of C=C bond in the side chain of the protein backbone. These characteristic FTIR features of collagen completely disappeared

upon Beta-radiation as indicated in Figure 5, curves b and c. Instead new IR absorbance bands were observed. The new evolved FTIR bands at 1149 cm^{-1}, 1080 cm^{-1}, 945 cm^{-1}, and 863 cm^{-1} are located in the fingerprint region which can be ascribed to destroyed organic fragments containing C=C-H, N-H, C-O groups. Their assignments are difficult. Nevertheless, these changes of the FTIR features in Figure 5 demonstrate clearly that the secondary structures of collagen and even the peptide chain have been destroyed by the Beta-radiation. Beta-radiation might result in disturbance of the triple helix conformation but it might also directly interfere with the amino acids involved in the interaction with platelets. The recognitions sites in collagen for the platelet receptors GPIaIIa and GPVI are GERGFO and (GPO)n, respectively. Because adhesion is clearly decreased but still aggregates are found the GPO sequence recognised by the activation receptor GPVI must be intact. The phenylanaline present in the GERGFO sequence is the first candidate that might be oxidized, and could contribute to the diminished adhesion after radiation therapy.

In summary, Beta-radiation treatment alters the reactivity of certain vessel wall extracellular matrix proteins, in particular vWF and collagen. These *in vitro* results offer an explanation how the thrombogenicity of vessels after beta-radiation decreases. The effect of beta-radiation on vWF was assessed by measuring the binding of domain-specific antibodies to treated surface vWF. The FTIR features demonstrate that the secondary structures of collagen have been destroyed by the Beta-radiation at 20 Gy. Beta-radiation might result in disturbance of the triple helix conformation but it might also directly interfere with the amino acids involved in the interaction with platelets. Thrombus propagation on disrupted plaque is a major cause of acute coronary events and serious complication after coronary intervention. The vessel wall may become lowly prone to thrombosis and resulting in decreased platelet adhesion and aggregation. It might help reduce the onset of acute coronary events and of acute coronary occlusion after the intervention.

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Abbreviations and Acronyms

ECM, extracellular matrix; GP, glycoprotein; HA, human albumin; HUVEC, human umbilical vein endothelial cells; PBS, phosphobuffered saline; vWF, von Willebrand factor, IVBT, Intravascular brachytherapy; FTIR, Fourier transform infrared spectroscopy;

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5

A randomized comparison of delayed and directly delivered intracoronary beta radiation in patients with in-stent re-stenosis: Six month angiographic and two years clinical follow-up of the OPTIRAD study

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BACKGROUND

Percutaneous coronary intervention (PCI) is the less invasive revascularization procedure, but is hampered by the need of repeated coronary interventions. The implantation of bare metal stents compared with balloon angioplasty reduced the risk of re-interventions significantly. However, 20-40% of the patients still needed one or more re-interventions within 12 months of bare metal stenting. The use of drug eluting stents in high-risk patients is beneficial but not fully elucidated yet [1,2]. The need of target vessel revascularization for bare-metal in-stent re-stenosis with two types of drug eluting stents varied from 8 to 19% within 6 months [3]. At the other hand, the incidence of re-stenosis is still increasing because more patients with multiple and complex lesions are currently accepted for PCI. Thus, there may be still an indication for additional options as intra-coronary radiation therapy (ICRT) for the treatment of in-stent re-stenosis [4-9]. The optimal timing of ICRT after PCI however is unknown. Hyperplasia of smooth muscle cells from the adventitia layer of the coronary artery wall is responsible for the process of in-stent re-stenosis. It is known from animal studies that smooth muscle cells entering the replicating phase between 48 to 36 hours after PCI are very vulnerable to ICRT [10-13]. We hypothesized that 48 hours delayed compared to directly delivered ICRT after PCI may be beneficial in patients with in-stent re-stenosis.

METHODES

Patient population

Patients referred for re-PCI to two tertiary centers in the Netherlands because of symptomatic bare metal in-stent restenosis of a native coronary artery were candidate for the study. Additional inclusion criteria were age between 18 and 80 years, coronary vessel diameter between 2.4 and 3.8 mm, lesion length < 52 mm and left ventricular ejection fraction > 35%. Main exclusion criteria were myocardial infarction within 72 hours before, prior radiation of the chest, females with childbearing potential and contra-indication for aspirin or clopidrogel. The ethics committee of both participating hospitals approved the trial. Written informed consent was obtained before randomization using the "closed envelope" method.

Procedure

Eligible patients underwent a pci within 7 days after randomization, via a femoral approach. Additional stent-implantation was allowed in case of acute occlusion, documented dissection or > 50% residual stenosis after balloon dilatation. After successful pci, angiographically defined by a residual stenosis < 30% and TIMI-flow 3, a baseline intracoronary ultrasound investigation (IVUS) was performed of the treated lesion, using a 30 MHZ system (Avanar® 5.64 – / Vulcano). The IVUS catheter was placed distal to the treated lesion to an easily recognizable landmark and withdrawn up to the guiding catheter with an automatic pullback system at a speed of 1.0 mm/s. The IVUS measurements were also used to determine the diameter of the balloon used for radiation therapy and in case of beta irradiation to determine the dosimetric calculations. The IVUS images were continuously recorded on S-VHS videotape and CD for off-line analysis.

Immediately after the IVUS procedure, the delivery catheter for radiation therapy containing a placebo source was used to check whether it was possible to advance and withdraw the catheter at the target lesion site, and to estimate of the length of the active radiation source required (minimum 23 mm, maximum 60 mm).

After irradiation, repeat angiography and IVUS examinations were performed after intracoronary injection of 0.2 mg nitroglycerin. ECGs were obtained immediately

after the procedure and the following morning. Creatine kinase and MB fraction were measured 8 and 20 hours after the procedure. Patients were treated with aspirin > 80 mg/day before pci. A bolus of 10,000 IU of unfractioned heparin was given intravenously after insertion of the femoral sheath, and repeated 5000 IU every 30 minutes after one hour. Clopidrogel 300 mg orally was started in the cathlab in case of implantation of a stent, followed by 75 mg daily for 6 months.

Radiation therapy

Patients received ICRT according to randomization immediately or 48 hours after a successful repeated PCI of the in-stent re-stenosis. A beta source for ICRT was used in both groups (Galileo® system from Guidant (Indianapolis, USA).

The dwell times were calculated in close consultation with the radiation oncologist with the aim to deliver one dose of 20 Gy at the adventitial layer. These values were in conformity with doses that have been shown to be effective in dose-finding studies, both in animal tests and in clinical application [4-6]. The radiation safety officer measured directly during the radiation therapy, the extent of radiation exposure at different sites in the catheterization lab. Patients randomized to direct radiation therapy were immediately radiated after the PCI procedure via a femoral approach. Patients in the delayed arm were discharged within 6 hours after a PCI via a radial approach. They were re-admitted within 48 hours to undergo ICRT via a femoral approach.

Quantitative angiographic analysis (QCA)

Angiography for QCA were performed in two orthogonal projections after radiation and at six months follow-up. The same projections were used each time. The images were recorded on CD and were analyzed quantitatively off-line. The analyses were performed, by an independent Core-lab. The minimal lumen diameters at the proximal and distal treated site and at the radiated site were assessed [15,16]. Late lumen loss was defined as the loss in difference in MLD between radiation time and 6 month follow-up. Binary stenosis was defined as > 50% diameter stenosis at the angioplasty site at 6 month follow-up.

Follow-up, end points and statistical analysis

Clinical follow-up was performed at 6, 12 and 24 months after ICRT. IVUS was performed immediately after radiation therapy and 6 month follow-up. Quantitative coronary angiography was determined at 6 months after ICRT. The primary goal of the trial was to compare the reduction of in-stent neointimal hyperplasia area by IVUS at 6 months between delayed and directly delivered ICRT. Secondary endpoints were binary restenosis as determined by QCA (stenosis of lumen > 50%) at 6 months, the risk of repeated target vessel coronary intervention and all cardiovascular events at 2 years after ICRT.

The sample size calculation was based on a reduction of neointimal hyperplasia area of 25% by delayed as compared with direct ICRT. The assumed standard deviation of neointimal hyperplasia at 6 months after direct beta radiation was set at 1.5 mm^2. With the alfa set at 0.05 and beta at 0.20 (power 80%), 60 patients were needed for this parallel comparison. A preliminary analysis was planned after the inclusion of the first 40 patients.

A myocardial infarction was defined by a rise of CKMB > 3 times the upper limit of normal and/or appearance of new Q-waves on the ECG.

All events after radiation therapy were recorded and analyzed by intention-to-treat. The clinical events were analyzed on the principle of the first event whichever comes first. Relative Risk (RR) with 95% confidence intervals (CI) will be used to express the risk of an event between the two groups. Dichotomous data were compared using the chi-square statistic. Means are presented with standard deviation (SD) and were compared using a two-sample t-test. Non-normally distributed continuous data are compared with the use of the Mann-Whitney test. Event-free survival was compared using a Kaplan-Meier analysis. Due to a relatively small number of patients included in this pilot study, differences in baseline characteristics might be occur despite of randomization. In addition we will also perform a multivariate regression analysis using the whole cohort of patients to adjust for baseline characteristics.

RESULTS

Between 2002 and 2003, the first 40 patients were included in the study. The baseline characteristics of these patients are shown in table 1.

Table 1. Clinical and angiographic characteristics of patients undergoing direct or delayed intracoronary beta radiation therapy

Variables	**Direct (N=20)**	**Delayed (N=20)**	**P-Value**
Mean age, year (SD)	60.9 (10.8)	62.5 (9.5)	0.59
Male	13 (65%)	15 (75%)	0.73
Myocardial infarction	4 (20%)	7 (35%)	0.30
Unstable angina	1 (5%)	1 (5%)	1.00
Current smoker	4 (20%)	2 (10%)	0.66
Hypertension	8 (40%)	9 (45%)	0.78
Hypercholesterolaemia	17 (85%)	16 (80%)	0.40
Diabetes	4 (20%)	4 (20%)	1.00
Left anterior descending artery	12 (60%)	11 (55%)	0.94
Left circumflex artery	2 (10%)	2 (10%)	0.94
Right coronary artery	6 (30%)	7 (35%)	0.94
Multivessel coronary disease (≥ 2 vessels)	12 (60%)	10 (50%)	0.41
Mean Lesion length, mm (SD)	21 (11)	20 (11)	0.70
Mean Lesion diameter, mm (SD)	2.8 (0.3)	2.9 (0.4)	0.37
Stent-implantation during radiation therapy	2 (10%)	5 (25%)	0.21

The distribution of the patients between the treatment groups was well balanced. All patients received the randomized treatment without any complications. The IVUS results at 6 month are shown in table 2. There was substantial differences in the parameters immediately after radiation (post radiation) in favour of the delayed group. However, there were no significant differences in the changes of neo-intimal hyperplasia between 6 month and post radiation.

Table 2. Intravascular ultrasound results after direct and delayed beta radiation

	Post radiation			Changes 6 month- post radiation		
Variables	**Direct (N=15)**	**Delayed (N=14)**	**P-value**	**Direct (N=15)**	**Delayed (N=14)**	**P-value**
Vessel area, edge proximal (mm^2)	15.1	17.2	0.35	1.67	-0.93	0.05
Lumen area, edge proximal (mm^2)	6.8	7.3	0.56	-0.52	-0.45	0.94
Vessel area, stent proximal (mm^2)	17.1	18.8	0.25	0.38	0.19	0.88
Lumen area, stent proximal (mm^2)	5.7	7.2	0.03	0.79	-1.00	0.07
Intimal hyperplasia area stent proximal(mm^2)	2.8	1.2	0.05	-0.11	0.63	0.26
Vessel area, stent mid (mm^2)	19.2	19.9	0.73	0.25	-1.12	0.24
Lumen area, stent mid (mm^2)	5.9	6.9	0.11	0.07	-0.71	0.14
Intimal hyperplasia, stent mid (mm^2)	2.7	1.2	0.05	0.09	0.85	0.23
Vessel area, stent distal (mm^2)	16.4	15.7	0.69	1.02	-0.22	0.19
Lumen area, stent distal (mm^2)	5.3	6.1	0.15	0.29	-0.20	0.19
Intimal hyperplasia, stent distal (mm^2)	2.0	1.1	0.06	-0.05	0.23	0.55
Vessel area, edge distal (mm^2)	14.1	13.2	0.82	0.64	-0.38	0.24
Lumen area, edge distal(mm^2)	5.2	6.0	0.28	0.93	-0.20	0.06

There were also no significant differences in binary stenoses with QCA at 6 month (table 3). The incidence of target vessel revascularization and cardiovascular events at 2 years were not different (table 4 and figure).

Table 3. Quantitative coronary angiographic results at 6 months after beta direct and delayed radiation

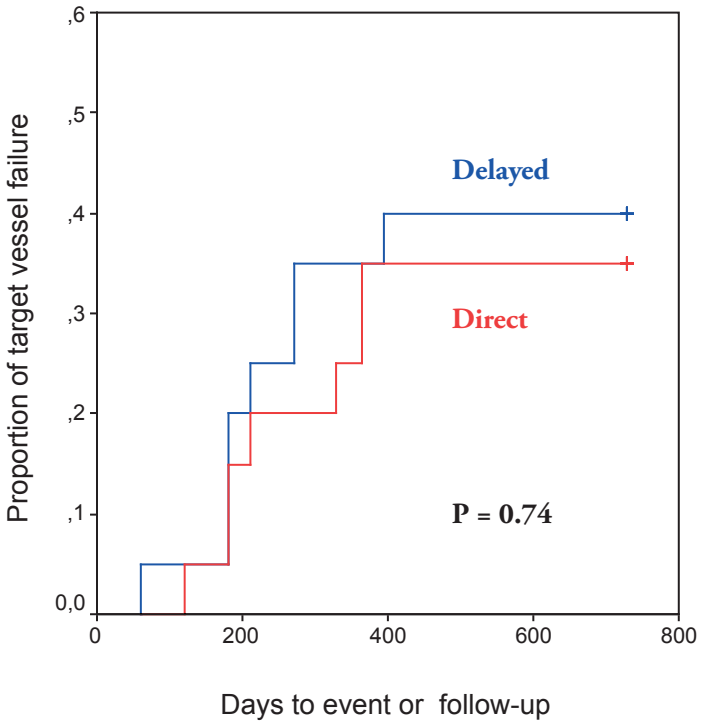
Variables	**Direct (N=17)**	**Delayed (N=15)**	**P-value**
Reference vessel diameter (mm)	2.70	2.82	0.28
MLD, proximal radiated site (mm)	2.58	2.83	0.17
MLD, mid radiated site (mm)	1.80	1.94	0.63
MLD, distal radiated site (mm)	2.52	2.69	0.30
Binary stenosis	12%	27%	0.28

MLD: minimal luminal diameter. Binary stenosis was defined as coronary lumen stenosis > 50% at follow-up.

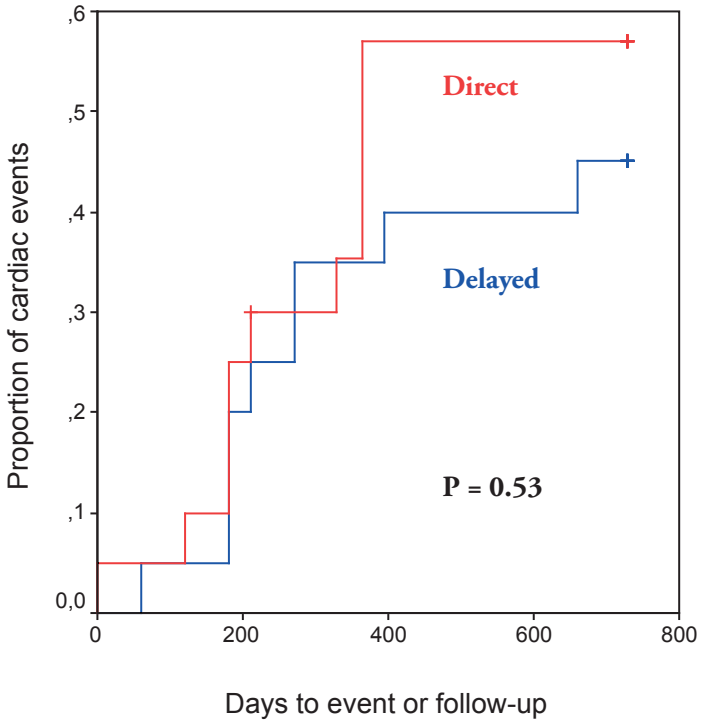
Table 4. Clinical events at two years after direct and delayed beta radiation

EVENT	Direct (N=20)		Delayed (N=20)		Relative Risk	95% CI	P Value
Death	1	(5%)	0	(0%)	NA	NA	0.31
Myocardial infarction, non-fatal	1	(5%)	1	(5%)	1.00	(0.07- 15.4)	1.00
Repeat coronary revascularization	9	(45%)	8	(40%)	1.13	(0.55-2.32)	0.75
Bypass surgery	3	(15%)	1	(5%)	3.00	(0.34-26.5)	0.29
Angioplasty	6	(30%)	7	(35%)	0.86	(0.35-2.10)	0.73
Target vessel failure	7	(35%)	8	(40%)	0.88	(0.39-1.95)	0.74
Lesion revascularization	3	(15%)	6	(30%)	0.50	(0.15-1.73)	0.25
Vessel revascularization	4	(20%)	2	(10%)	2.00	(0.41-9.71)	0.37
Any event	11	(55%)	9	(45%)	1.22	(0.65-2.29)	0.53
Free from events	9	(45%)	11	(55%)	0.82	(0.44-1.53)	0.53

Values are numbers of patients, with percentages in parentheses. CI denotes confidence interval.



Proportion of patients with target vessel failure (repeated revascularization or myocardial infarction).



Proportion of patients with cardiac events

DISCUSSION

This two center randomized clinical trial showed no benefit of delayed over direct delivered intra-coronary radiation therapy in patients with bare metal in-stent restenosis. The present paper contains the results of the pre-specified analysis of the first 40 patients included. There were no significant differences between the treatment groups in terms of intravascular outcomes at 6 month, and it was not expected that the inclusion of 20 more patients would have changed these results. Therefore the inclusion of patients was prematurely stopped. One major limitation of the present analysis is the incomplete participation of the patients in the 6 month IVUS analysis. IVUS assessments were not performed in more than 25% of the included patients. Most of these patients

refused control angiography and thus IVUS because of absence of angina. However, the distribution of the incomplete IVUS data were well-balanced (table 2). One may hypothesize that the time point of IVUS assessment was not appropriately choosen to detect the benefit of delayed radiation therapy. The time point of 6 month after radiation was chosen according to previously published data [13-18]. The eventually missed beneficial IVUS results have not been translated into benefit in terms of clinical outcome (table 4). The clinical analysis concerns a 100% complete 2 years follow-up.

There is scarce data from animal studies showing beneficial effect of delayed radiation therapy, and there is no data at all from patients[10-12]. The process of neo-intimal hyperplasia in animals may differ substantially from humans. The time point of radiation delivery may not be appropriately choosen, because the replicating phase of involved cells in patients with athrerosclerosis may be totally different than in non-atherosclerotic animals. Therefore more data from animal studies and patients as well are needed to elucidate the possible beneficial effect of delayed intracoronary radiation therapy.

CONCLUSIONS

In patients with bare metal in-stent re-stenosis, delayed compared to direct beta ICRT showed no benefit in terms of clinical outcome or intracoronary ultrasound and angiographic outcomes.

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6

A randomized comparison of intracoronary drug eluting stent implantation versus beta and gamma brachytherapy in patients at high risk of coronary restenosis. Long term clinical, angiographic and intravascular ultrasound outcomes of the BEGUT Trial.

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INTRODUCTION

Percutaneous coronary intervention (PCI) is the preferred initial revascularization strategy in patients with coronary artery disease [1]. Despite its efficacy in reducing symptoms, PCI is hampered by the need of repeat coronary interventions. The implantation of bare metal stents (BMS) reduced the incidence of recurrent stenosis due to in-stent restenosis (ISR), but still 20-30% of patients require additional coronary interventions within 12 months [2]. Among many other factors, diabetes and re-stenosis of previous treated coronary segments [3] have been identified as key determinants of in ISR after BMS. The issue of re-stenosis is currently being addressed by other treatment modalities, such as intra-coronary brachytherapy (BT) [4] and drug eluting stents (DES) [3]. Previous clinical studies demonstrated that PCI supplemented by BT leads to a significant reduction of re-stenosis especially in patients with ISR. [4 – 7]. Two types of radiation emitters, beta and gamma, are used for catheter based BT. A gamma compared to a beta emitter, requires additional radiation protection measures in the catheterization laboratory. It has been hypothesized that the more consistent and penetrating distribution of radiation with the gamma emitter may improve its anti-proliferative effect on the vessel wall. No direct comparison between these two sources of BT has been reported so far. The aim of the present study was to directly compare the effectiveness of DES to both beta BT (ß-BT) or gamma BT (γ-BT) in patients undergoing PCI with an expected high risk of re-stenosis.

PATIENT

Patients between 18 and 75 years old scheduled for PCI of a single lesion in a native coronary artery were eligible provided they had a re-stenosis within 1 year after PCI (balloon or stent) and/or type C lesion and/or were on medical treatment for diabetes. Main exclusion criteria were vessel diameter less then 2.5 mm or more then 4.0 mm, lesion length exceeding 22 mm, completely occluded vessel, unstable angina (Braunwald 3 A/C), contra-indication for aspirin or clopidrogel, prior chest radiotherapy and pregnancy. The ethics committee of the University Medical Center Utrecht approved the

study protocol. Written informed consent was obtained before randomization to beta/gamma radiation or DES by sealed envelopes.

TREATMENT

PCI was performed within 7 days after informed consent was obtained, via the femoral approach and standard practice. Stent-implantation was performed in case of acute vessel closure or angiographically visible dissection or > 50% residual stenosis after balloon dilatation. After successful PCI (residual stenosis < 30% and TIMI-flow 3 by visual assessment), intracoronary ultrasound investigation (IVUS) was performed of the treated segment (Avanar® 5.64 – / Vulcano™, 30 MHZ, motorized pullback 1 mm/sec). IVUS was used for the determination of the diameter of the balloon used for radiation and dosimetric calculations in case of beta therapy and for the assessment of the changes in the lumen and vessel wall dimensions at 6 months after radiation. IVUS images were continuously recorded on S-VHS videotape and CD for off-line analysis.

Immediately after IVUS assessment, a delivery catheter for radiation therapy containing placebo was used to check the feasibility to safely advance and withdraw the (active) catheter at the lesion site, and to estimate the length of the active irradiation source required (minimum 23 mm, maximum 60 mm). The beta source used consisted of the Galileo® system (Guidant Indianapolis, USA) and the gamma of Checkmate® (Cordis J&J, Miami, USA). The respective dwell times were calculated by the radiation oncologist with the aim to deliver a dose of 20 Gy at the adventitial layer in the case of beta irradiation and 16 Gy at a distance of 2 mm from the source in case of gamma irradiation which have been shown to be effective in experimental and clinical dose-finding studies. BT was administered unfractionated except in case of hypotension or ischemia. After irradiation, repeat angiography in two orthogonal projections and IVUS examinations were performed after intracoronary injection of 0.2 mg nitroglycerin.

A first generation DES was used, based on a stainless steel balloon expandable stent coated with sirolimus (Cypher). The stent was designed to release approximately 80% of

its sirolimus within 30 days after implantation. Patients were treated with aspirin > 80 mg/day and clopidrogel (300 mg loading dose) followed by 75 mg daily for only two months.

End points and statistical analysis

Patients were seen at the out-patient clinic at 6, 12, 24 and 36 month after the index therapy. QCA and IVUS were performed immediately after therapy and at 6 month angiographic follow-up. The primary clinical endpoint was the proportion of target vessel failure defined by all-cause death, target vessel revascularization and target vessel related myocardial infarction at three years. The secondary clinical endpoints were the proportion individual clinical events.

The angiographic endpoint was defined by the binary restenosis rate (> 50% diameter stenosis) at 6 months with quantitative coronary angiographic analysis (QCA). The QCA were performed, by an independent Core-lab (Diagram-Zwolle) blinded for treatment allocation. Late lumen loss was defined as the loss in difference in MLD directly after the index treatment and 6 month follow-up.

Change in vessel and lumen area directly after the index treatment and 6 month follow-up at the proximal, mid and distal end of the treated site was compared using intravascular ultrasound.

The main analysis consisted of the comparison of the primary and secondary endpoint between the three groups on basis of intention-to-treat. The clinical events were analyzed on the principle of the worst event in descending order of severity and expressed by the relative risk (RR) with 95% confidence intervals (CI). Dichotomous data were compared using the chi-square statistic. Means are presented with standard deviation (SD) and were compared using a two-sample t-test. Non-normally distributed continuous data were compared using the Mann-Whitney test. Event-free survival was compared using Kaplan-Meier analysis.

RESULTS

The baseline characteristics of the patients are shown in table 1. Diabetes was more prevalent in the ß-BT group while there were more patients with complex lesion morphology in the gamma group. Additional stents were implanted in 12 patients in each group (Table 1). All patients received the allocated type of BT. The dose and the mean time of delivery of ß-BT or γ-BT radiation were 20 versus 16 Gray and 3.8 versus 21.7 minutes, respectively. There were no clinical events neither during the procedure nor during the hospital stay.

Table 1. Baseline clinical and angiographic characteristics of patients undergoing intracoronary beta or gamma brachytherapy (BT) or implantation of drug eluting stent (DES).

Variables	**ß-BT (N=40)**	**γ-BT (N=40)**	**DES (N=40)**	**P-Value DES vs ß-BT**	**P-Value DES vs γ -BT**
Mean age ± SD, Y	61.1 (11.5)	59.4 (8.1)	59.7 (9.1)	0.54	0.87
Male, (%)	32 (80)	32 (80)	31 (78)	0.78	0.79
Myocardial infarction, (%)	5 (13)	9 (23)	11 (28)	0.09	0.61
Unstable angina, (%)	1 (3)	2 (5)	2 (5)	0.56	1.00
Current smoker, (%)	11 (28)	7 (18)	12 (30)	0.81	0.19
Hypertension, (%)	20 (50)	15 (38)	13 (33)	0.11	0.64
Hypercholesterolaemia, (%)	34 (85)	30 (75)	28 (70)	0.11	0.62
Diabetes, (%)	18 (45)	7 (18)	14 (35)	0.36	0.08
Left anterior descending artery(%),	18 (45)	16 (40)	18 (45)	1.00	0.56
Left circumflex artery, (%)	7 (18)	11 (28)	7 (18)	1.00	0.56
Right coronary artery, (%)	15 (38)	13 (33)	15 (38)	1.00	0.56
Type B2 and C coronary lesions, (%)	24 (60)	34 (85)	32 (80)	0.05	0.36
Coronary lesion length, mm	15 (9.0)	21 (9.0)	17 (9.0)	0.31	0.04
Coronary vessel diameter, mm	2.9 (0.4)	2.8 (0.4)	2.8 (0.4)	0.10	0.67
Previous PCI of target segment, (%)	25 (63)	26 (66)	28 (70)	0.48	0.63

The clinical data of the 3 years follow-up is summarized in Table 2 and figure. The primary endpoint (target vessel failure at 3 years) was observed in a lower proportion of patients who received DES as compared with ß-BT or γ-BT (15% vs 45% vs 30%). The primary endpoint when comparing ß-BT to γ-BT (30% vs 45%, p=0.34) was in favour of γ-BT, without reaching the level of statistical significance. Two patients suffered from a stent thrombosis (one at 6 weeks following ß-BT and one at 4 months after γ-BT).

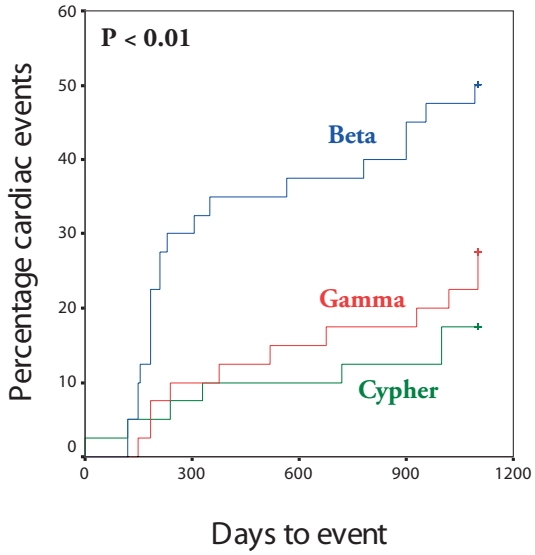
Table 2. Cardiac events at 3 years after beta or gamma brachytherapy or cypher stenting

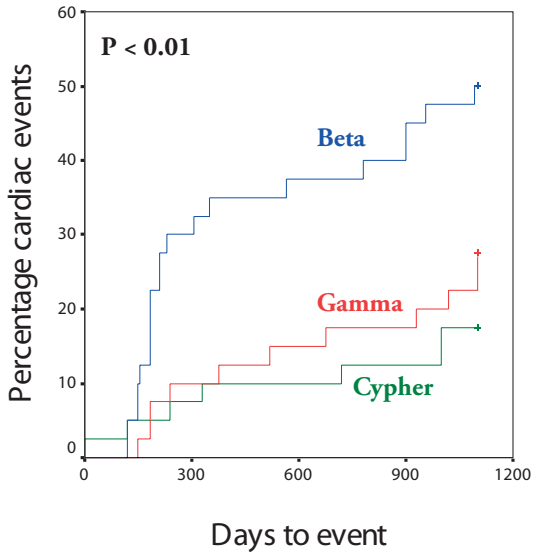
EVENT	**ß-BT (N=40)**		**γ-BT (N=40)**		**DES (N=40)**		**P-Value DES vs ß-BT**	**P-Value DES vs γ -BT**
Death	1	(2.5%)	1	(2.5%)	0	(0.0%)	NS	NS
Myocardial infarction, non-fatal	2	(5.0%)	2	(5.0%)	1	(2.5%)	0.88	0.88
Coronary re-intervention	13	(32.5%)	9	(22.5%)	5	(12.5%)	0.03	0.24
Bypass surgery	4	(10.0%)	4	(10.0%)	1	(2.5%)	0.17	0.17
Angioplasty	9	(22.5%)	5	(12.5%)	4	(10.0%)	0.13	0.72
Target vessel failure	16	(45.0%)	12	(30.0%)	6	(15.0%)	0.01	0.11
All events†								
Death	1	(2.5%)	1	(2.5%)	0	(0.0%)	NS	NS
Myocardial infarction, non-fatal	3	(7.5%)	2	(5.0%)	1	(2.5%)	0.67	0.93
Stent thrombosis	1	(2.5%)	1	(2.5%)	0	(0.0%)	NS	NS
Coronary re-intervention	23	(57.5%)	14	(35.0%)	5	(12.5%)	0.02	0.04
Bypass surgery	6	(15.0%)	4	(10.0%)	1	(2.5%)	0.06	0.35
Angioplasty	17	(42.5%)	10	(25.0%)	4	(10.0%)	0.04	0.07
Target vessel failure	16	(40.0%)	10	(25.0%)	4	(10.0%)	0.03	0.06
Death	1	(2.5%)	1	(2.5%)	0	(0.0%)	NS	NS
Lesion revascularization	11	(27.5%)	4	(10.0%)	1	(2.5%)	0.05	0.08
Vessel revascularization	4	(10.0%)	5	(12.5%)	2	(5.0%)	0.23	0.15
Myocardial infarction	1	(2.5%)	1	(2.5%)	1	(2.5%)	1.00	1.00

Values are numbers of patients, with percentages in parentheses. CI denotes confidence interval.

*Worst events: in descending order of severity.

†All events were included. For example, in the beta- group, one patient underwent an angioplasty and bypass surgery after the index treatment. In this patient, both events (angioplasty and bypass surgery were counted.





Legends

Bottom panel: proportion of patients with target vessel failure (target vessel repeated revascularization or myocardial infarction).

Top panel: proportion of patients with any cardiac event (death, myocardial infarction or additional coronary revascularization).

The QCA and IVUS findings at 6 months were in favour of both types of BT as compared to DES (table 3 and 4). These findings were in concordance with the clinical outcome defined by target failure revascularization at 6 months, DES vs ß-BT or γ-BT: 5.0% vs 2.5% vs 0.0%, respectively.

Table 3. Quantative coronary angiographic results directly and 6 month after beta or gamma brachytherapy and drug eluting stenting

Variable	**Baseline (after intervention)**			**Difference in MLD (6 month versus baseline)**				
	ß-BT (N=40)	**γ-BT (N=40)**	**DES (N=40)**	**ß-BT (N=38)**	**γ-BT (N=39)**	**DES (N=38)**	**P-Value DES vs ß-BT**	**P-Value DES vs γ -BT**
Reference diameter (mm)	2.86	2.81	2.93	-0.03	-0.05	+0.01	0.73	0.53
MLD, proximal (mm)	2.96	2.88	2.95	+0.06	+0.12	+0.13	0.47	0.95
MLD, mid (mm)	2.89	2.75	2.88	-0.01	+0.22	+0.51	0.01	0.05
MLD, distal (mm)	2.75	2.74	2.81	+0.18	+0.16	+0.25	0.62	0.52
Binary stenosis, %	-	-	-	12.5	10.0	5.0	0.24	0.40

MLD: minimal luminal diameter. Difference in MLD indicates loss (+) or gain (-)of MLD of the treated segment at 6 month compared to baseline. Binary stenosis was defined as > 50% lumen stenosis at follow-up angiography. All diameters are expressed in mm.

Table 4. Intravascular ultrasound results directly and 6 month after beta or gamma brachytherapy and drug eluting stenting

Variables	**Baseline (after intervention)**			**Difference (6 month versus baseline)**				
Vessel or lumen (area, mm2)	**ß-BT (N=36)**	**γ-BT (N=37)**	**DES (N=36)**	**ß-BT (N=32)**	**γ-BT (N=34)**	**DES (N=33)**	**P-Value DES vs ß-BT**	**P-Value DES vs ß-BT**
Vessel, proximal edge	16.3	15.1	16.1	+0.30	+1.01	-0.12	0.25	0.03
Lumen, proximal edge	7.6	6.9	8.5	+0.07	+0.40	-0.14	0.60	0.31
Vessel, proximal treated	16.7	16.4	16.9	+1.34	+0.92	+0.08	0.03	0.05
Lumen, proximal treated	6.5	6.6	6.4	+0.17	+0.15	-0.08	0.34	0.36
Vessel, mid treated	16.5	16.0	16.6	+2.22	+0.94	+0.45	0.02	0.46
Lumen, mid treated	6.2	5.4	6.1	+0.90	+0.17	-0.04	0.08	0.82
Vessel, distal treated	15.1	14.1	14.8	+2.17	+1.22	+0.64	0.05	0.38
Lumen, distal treated	6.4	5.2	6.1	+0.15	+0.52	-0.05	0.51	0.06
Vessel, distal edge	12.5	12.7	12.7	+1.30	+0.80	+0.22	0.12	0.33
Lumen, distal edge	6.1	5.6	6.4	+0.06	+0.10	+0.16	0.26	0.27

Loss (-) or gain (+) of area at 6 month versus baseline.

DISCUSSION

The present study demonstrates the difficult management of patients with coronary artery disease at high risk of recurrent stenosis after PCI. The angiographic and IVUS data at 6 months were in favour of BT. However, at 3 years, the clinical outcome after DES was superior to both types of BT. The 3 years clinical outcome was somewhat in favour of γ-BT as compared to ß-BT. To appreciate these findings, some features of the study need to be clarified.

Numerous modalities of therapy for ISR have been advocated, such as laser therapy, bare metal stenting, drug eluting stenting and brachytherapy. All these therapy modalities have advantages and disadvantages. We have investigated the role of two types of BT and DES in this field. Various studies have demonstrated the early safety and efficacy for both beta and gamma radiation for in stent restenosis [4-8]. However data regarding the outcome beyond 12 months follow-up are limited. The present study shows that BT using a gamma source is feasible and safe in a setting of a routine catheterization laboratory.

The angiographic and IVUS data at 6 months after intervention were in favour of BT. This was in concordance with the clinical outcome at 6 months. The dramatic increase of the proportion of target vessel failure after both ß-BT and γ-BT may reflect the phenomenon of late catch-up, as postulated previously [9]. This suggests that the process of neointimal hyperplasia leading to re-stenosis starts at a later stage after BT, than is known after PCI with or without stent-implantation. Although no planned angiographic follow-up was scheduled, beyond 6 months, the ischemia driven angiographic data strongly suggest the occurrence of this phenomenon at long-term follow-up. Based on the IVUS data at follow-up there seems to be already a trend towards more lumen loss at the edges of the segments treated by ß-BT. The present study shows the relevance of long-term clinical follow-up in stead of short-term surrogate outcome after novel therapies. The high incidence of target vessel revascularization rate after ß-BT in the present trial is in agreement with a recent report of ß-BT after 2 years follow-up[10] .

One of the major concerns using BT is the occurrence of sub-acute thrombosis (SAT) [11,12]. At the time the study was started, little was known about SAT. According to current standards, a very conservative anti-platelet regimen was prescribed of only 2 months of dual anti-platelet therapy after DES or BT. Remarkably, we found a low number of clinical SAT in the BT group, and none in the DES group. Just two patients presented with a SAT, one 6 weeks after gamma therapy after prematurely stopping clopidogrel at week 4, one in the beta arm 4 month after the index procedure. It is conceivable that SAT has been prevented because of nice angiographic result with use of IVUS. Since the incidence of SAT was very low it was of little impact on TVF.

The results of the present study demonstrate a clear long-term benefit of DES over BT in patients at high risk of restenosis. Considering this outcome DES should be recommended as a first choice revascularization strategy in patients eligible for stent-implantation and at high risk of re-stenosis. This strategy is common in most clinics nowadays in the absence of a percutaneous alternative treatment modality. It has been clearly demonstrated that in comparison to BMS, DES reduces in-stent hyperplasia effectively [2] and concordantly the need for repeat revascularizations both in low [13] and high-risk patients [3]. However, there is uncertainty regarding the safety of DES on the long term. In particular the incidence of late stent thrombosis because of incomplete re-endothelialization of the stent has been criticized. It has been postulated that stent thrombosis is associated with discontinuation of dual anti-platelet therapy. A recent report however shows a constant incidence of stent thrombosis after DES in daily practice patients of 0.6%/year while on dual anti-platelet therapy [14]. The long-term benefit of novel treatment modalities in the prevention of ISR like drug eluting balloon [15] or bio-absorbable stents [16] has to be proven. Low energy gamma emitting stents might be beneficial as well as recently published by Kutryk etal.[17]. The management of another group of patients with ISR after the use of DES is unknown. The use of brachytherapy maybe beneficial, as shown in a recent report using ß-BT [18]. According to the long-term results of the present study, γ-BT is superior to ß-BT. These novel treatment modalities should be tested extensively and on the long-term in animal models, before introducing it in the clinical setting. Coronary bypass grafting for patients at high risk for re-stenosis should also be considered,

despite its more invasive nature. In particular patients with multi-vessel disease, diabetes and impaired left ventricular function may benefit from bypass grafting [19].
The most important limitation of the present study concerns the low number of patients included, reflecting the difference in baseline characteristics such as diabetes, especially between the BT groups. Overall the patients in the DES group had a higher risk-profile than in both BT groups. Therefore, the superior long-term clinical outcome of DES is valid and in agreement with other studies.

CONCLUSION

In patients with a high risk for restenosis after PCI, drug eluting stent implantation compared to beta or gamma brachytherapy is associated with a better long-term clinical outcome, despite a worse short-term angiographic outcome.

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7

Remise in the treatment of in-stent Restenosis

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For patients and interventional cardiologists, restenosis has been a major disappointment in the field of percutaneous, transluminal coronary angioplasty (PTCA) and patients with restenosis have suffered both physically as well as emotionally. The early spectacular results of treatment gradually faded away within three months and 6–12 months since the introduction of the intra-coronary stent. It is difficult to find a cardiologist who does not have patients that have been psychologically affected by one or more restenotic events. For the physician, the mechanism and potential prevention of the problem remains obscure although many approaches have been developed to protect treated vessels from excessive wound healing that leads to eventual luminal diameter reduction and clinical symptoms of angina. Many pharmacological, and even gene therapy, trials were extremely successful in animal models, but failed to deliver in the atherosclerotic human coronaries. The potential genetic predisposition and co-morbidity have been analysed in order to identify patients at risk from this serious complication, with variable outcome (GENDER: GENetic DEterminants of Restenosis Dutch Multicenter study). Although, the introduction of stents have reduced and delayed the development of restenosis, the problem has not been solved.

Potentially, the problem might be minimised by the introduction of the drug-eluting stents (DES) that are currently being used on a large scale in the US, but in a selected number of cases in Europe for various reasons. Among the reasons to restrict the use of DES are economical considerations and a modest increase in sub-acute and late in-stent thrombosis. Although the occurrence rate of DES thrombosis is low, the presentation of this acute problem is impressive as electively treated patients develop an acute myocardial infarction with a high rate of anterior wall infarctions.

These considerations cause in-stent restenosis (ISR) to remain a serious problem that deserves our on-going attention and research efforts. The study reported by Radke et al.,[1] is therefore an important contribution addressing the treatment of ISR. In this study, two comparable populations are described, treated either with DES (paclitaxel) or intra-coronary ß brachytherapy (ICBT). Both approaches appeared to be equipotent and rather successful for the treatment of ISR, therefore remise is the outcome here.

The current treatment modalities for ISR include repeat balloon angioplasty, repeat stenting, cutting balloon angioplasty, directional coronary atherectomy, rotational coronary atherectomy, brachytherapy, and DES. To judge a study on its merits, the first question is whether the most optimal treatment strategies were compared. Therefore, it is important to determine which DES has the best results in ISR. Paclitaxel-coated stents are available in a moderate and slow-release form. Only one release form and stent coated with sirolimus is available. Although DES are being used in clinical practice to treat ISR successfully, no direct comparison is available that shows superiority of one stent.[2,3] For radiation therapy γ and ß sources are available and both have been successfully applied to treat ISR with comparable outcome.[4] No important differences were reported in the routine clinical application of γ or ß radiation in single centre registries.[5]

Based on these studies, the approach of comparing radiation therapy with DES by Radke et al., appears to be rational. An important limitation of the study, however, is its size and design as patients were retrospectively matched from two databases and the angiographic analysis performed after 6 months, whereas another clinical evaluation was performed after 12 months. A significant difference was observed for the minimal luminal diameter ($P<0.01$) and in-stent net gain ($P<0.04$) favouring DES. Other parameters also hinted at a trend, both morphological and clinical, towards better results after DES implantation. The fact that the DES is easy to use and does not require any special adjustments in the catheterisation laboratory would also support its use in ISR. Fortunately, we are moving from high recurrence rates after percutaneous transluminal rotational ablation of 64.9% and 51.2% after rePTCA in the ARTIST study to values of 20% after DES and 16% after ICBT, but it is obvious that 20% recurrence of ISR is still a major clinical problem. Potentially, the combined approach (DES with ICBT) could reduce the recurrence rates even further. This will depend on whether different molecular targets can be reached with drugs interfering in the cell cycle and the exact effect of radiation on tissue healing.

Therefore, our focus must be on the prevention of ISR through risk stratification and tailored therapy for PTCA patients, within the limits of budget constraints. A potential quick and inexpensive solution could have been the introduction of direct stenting.

However, the published results are disappointing as they show near identical ISR rates compared directly with conventional stenting. The feasibility of using DES in patients with increased risk for ISR has already been reported by several groups with clinical events in <5% of the cases. Another approach is to compare different treatments in the high risk patients for preventive measures such as ICBT or DES. One example of a recently completed randomised trial is the BEGUT (The BEta versus Gamma Utrecht Trial)-Cypher study.[6] In this single centre prospective trial, patients were included if they had a high risk for restenosis >40%, or ISR. ISR risk assessment is based on treatment for diabetes and/or type C-lesions according to AHA/ACC classification. In the trial, high risk patients were randomised to either DES (sirolimus), ß (P32-*Galileo-Guidant*) or γ-irradiation using the Checkmate (*Cordis J & J*, Miami, USA) device. Forty patients were included in all arms. All three systems were used as they have been shown to provide excellent acute results. These techniques have also been shown to induce positive remodelling and inhibition of (in-stent)-hyperplasia/tissue growth at 6-month follow-up in earlier studies. Such direct comparative studies should help us select the correct therapy for each individual patient. Further tailoring will require the re-evaluation of potential additional pharmaceutical treatment looking at anti-coagulant therapy, and AT1 blockers, ACE inhibitors, statins and calcium antagonists.

In the near future, patients will have to be classified on the basis of biochemical markers of inflammation, genotype, co-morbidity and lesion characteristics to determine the risk of ISR in one individual patient. The outcome of the classification will determine which therapy is most appropriate and also where coronary bypass surgery has to be considered. Before we can make definite therapy choices for the best initial treatment, additional studies are required on the long-term outcome with respect to angiography and clinical end-points of high risk patients for the development of ISR. In the meantime, it is comforting that the risk for a recurrence of ISR has been reduced by more then 50% and that we have devices that can be used in every centre to improve our treatment in the unfortunate patients with symptoms due to in-stent tissue growth.

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Stent thrombosis in real world patients: a comparison of drug-eluting with bare metal stents

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ABSTRACT

Background

Although the introduction of drug-eluting stents (DES) has been associated with an impressive reduction in target vessel revascularization, there has been concern about the safety profile. The aim of this study was to determine the incidence of stent thrombosis in real world patients and evaluate the contribution of drug-eluting stents.

Methods

A prospective observational cohort study was conducted at a high-volume center in Utrecht, the Netherlands. All patients that underwent a percutaneous coronary intervention (PCI) between January 1st and December 31st 2005 were evaluated. The patients were pretreated with aspirin and clopidogrel, which was continued for 6 months in bare metal stents (BMS) and 12 months in DES.

Results

In 2005, 1309 patients underwent a PCI procedure with stent implantation. After a median follow-up of 9 months, 1.8% (n = 23) of the patients suffered from stent thrombosis. Two cases could be attributed to incorrect use of anti-platelet agents. In 8/23 cases, a technical reason was found such as an unrecognized dissection or stent underexpansion. The timing of stent thrombosis was acute in 1/23 patient, subacute in 20/23 patients and late in 2/23 patients. In both cases of late stent thrombosis, a BMS had been used. There were no differences in stent thrombosis rates between DES and BMS (1.4% vs. 1.9%, ns.). This is remarkable since DES were used in more complex and longer lesions.

Conclusion

The use of DES in routine daily practice appears not to be associated with a higher rate of stent thrombosis than BMS.

INTRODUCTION

The introduction of drug-eluting stents has been associated with an impressive reduction in target vessel revascularization. This has led to a rapid and widespread adoption throughout the world. However, there has been concern about the safety profile[1]. The most dramatic outcome is stent thrombosis, a condition associated with a high mortality rate. In 2003, the FDA published a web notification after receiving numerous reports of subacute stent thrombosis with the sirolimus-eluting stent[2]. Theoretically, this may be expected because of the combination of delayed endotheliazation of the drug-eluting stent with an increased tendency to platelet aggregation on sirolimus[3,4]. The randomized clinical trials, although carried out in selected patients with a relatively short follow-up, could not confirm the suspicion raised[5-7]. The question remains whether drug-eluting stents can be applied safely in real-world patients with more complex lesions. The aim of this study was to determine the incidence of stent thrombosis in an unselected cohort of patients and evaluate the contribution of drug-eluting stents.

PATIENTS AND METHODS

A prospective observational cohort study was conducted at a high-volume center in Utrecht, the Netherlands. All patients that underwent a percutaneous coronary intervention (PCI) between January 1st and December 31st 2005 were evaluated. The indications for PCI included stable angina pectoris, unstable angina (NSTE-ACS) and acute myocardial infarction (STE-ACS). We applied the following criteria for the use of drug-eluting stents (DES): In-stent restenosis, long lesions (> 20 mm), vessel diameter < 3 mm and diabetes mellitus[8]. DES usage was discouraged in STE-ACS and poor patient compliance.

In case of elective PCI procedures, the patients were on 100 mg aspirin and 75 mg clopidogrel daily for at least one week before the procedure. Emergency PCI was carried out by administration of a loading dose of 450 – 900 mg aspirin intravenously, 300 – 600 mg clopidogrel orally and an intravenous bolus of 5000 units of unfractionated heparin.

At the start of the PCI, a weight-adjusted initial dose of 70 U/kg of unfractionated heparin was administered. GPIIbIIIa-inhibitors (tirofiban and abciximab) were used at the discretion of the interventionalist. Aspirin was continued indefinitely and clopidogrel for 6 months in case of bare metal stents and 12 months in drug-eluting stents. Angiographic and procedural outcome were documented by the interventional cardiologist. The clinical outcome was recorded by the clinician at the ward before dismissal. Clinical follow-up was carried out for an average of 9 months (range 3-15 months). In case of complications, medical records at our hospital and elsewhere were reviewed to characterize clinical events during the study period.

Stent thrombosis was defined as the occurrence of, angiographically confirmed, partial or total stent occlusion or sudden cardiac death after successful stent implantation. Stent thrombosis was categorized according to the timing of occurrence into acute (< 1 day), subacute (1-30 days) and late (> 30 days). The cases with stent thrombosis were reviewed by a panel of 3 interventionalists to evaluate technical aspects of the PCI procedure. The following technical aspects were scored: stent expansion, sidebranch event, dissection and residual stenosis > 50% in the treated segment. In addition, we evaluated the medical records to document drug prescription during hospital stay and at dismissal, as well as patient adherence to medication.

Categorical variables were compared by the χ^2 test or the Fisher exact test. Continuous variables are presented as mean ± SD and were compared with the use of the Student *t* test. All statistical analyses were carried out with the software package SPSS version 11.5.0.

RESULTS

Baseline characteristics

In 2005, 1384 patients underwent a PCI procedure. Seventy-five patients were excluded because no stent was implanted. The reason was either balloon angioplasty only or an unsuccessful recanalization. Thus, 1309 patients were included in the cohort. The patients were followed for an average of 9 months. The mean age of the whole group was 63 ± 12

years (Table 1). The indication for the PCI was stable angina in 48%, a NSTE-ACS in 23% and a myocardial infarction in 27%. Nineteen percent of the patients were diabetic. With regard to lesion characteristics, 42% of the interventions was performed in a type A or B1 lesion whereas 58% concerned a type B2 or C lesion. GPIIbIIIa-inhibitors were administered in 23% of the procedures.

Table 1. Baseline characteristics

	Overall (n=1309)[2]	**BMS (n=1015)**	**DES (n=294)**	**P value[1]**
Age (years)	63±12	63±12	61±11	0.036
Male sex	0.74	0.74	0.73	ns
Indication				
-Stable angina pectoris	0.48	0.44	0.65	0.000
- NTSE-ACS	0.23	0.24	0.22	ns
- STE-ACS	0.27	0.31	0.12	0.000
Multivessel PCI	0.12	0.11	0.17	0.009
Current smoking	0.61	0.64	0.48	0.007
Hypercholesterolaemia	0.50	0.49	0.53	ns
Hypertension	0.45	0.44	0.51	ns
Diabetes	0.19	0.11	0.42	0.000
Positive family history	0.48	0.47	0.50	ns
Renal dysfunction	0.15	0.13	0.18	ns
Previous MI	0.26	0.25	0.32	0.015
Previous PCI	0.20	0.22	0.41	0.000
Previous CABG	0.06	0.06	0.07	ns
Good LV function	0.78	0.78	0.79	ns
Procedural characteristics				
Segments, no.	1681	1321	360	
Vessel				
- Left main	0.01	0.01	0.01	ns
- Left anterior descending	0.42	0.38	0.55	0.000
- Right circumflex	0.23	0.24	0.20	ns
- Right anterior descending	0.33	0.35	0.23	0.000
- Graft	0.02	0.02	0.01	ns
Lesion characteristics				
- Type A/B1	0.43	0.46	0.30	0.000
- Type B2/C	0.57	0.54	0.70	0.000
TIM1 3 flow	0.70	0.70	0.73	ns
Thrombus	0.25	0.29	0.12	0.000
GP IIb/IIIa-I	0.23	0.25	0.17	0.004
Stent thrombosis	0.018	0.019	0.014	ns

[1] The probability value refers to the difference between the drug-eluting stent (DES) and the bare metal stent (BMS) group. [2] 75 out of 1384 patients were treated with balloon angiopasty or attempt to recanalisation, without the use of stents; this results in a study cohort of 1309 patients. NTSE-ACS=unstable angina, STE-ACS=acute myocardial infarction, MI=myocardial infarction, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft, LV=left ventricle.

Drug-eluting stents

In accordance with the indications for DES use in our center, DES were predominantly used in patients with stable angina pectoris, diabetics and multi-vessel procedures. With regard to lesion characteristics, DES were used more often in complex lesions and more frequently involved the LAD. On the other hand, the RCA was treated more frequently with BMS.

Stent thrombosis

Stent thrombosis occurred in 1.8% of the patients (23/1309). The DES group demonstrated a stent thrombosis rate of 1.4% and the BMS group 1.9% (n.s.). The only variables that differed significantly between the group with and without stent thrombosis were age and target vessel (table 2). The stent thrombosis group was older and more frequently associated with a PCI of the LAD. Although there was a tendency towards a higher frequency of renal dysfunction, diabetes and poor LV function in the group with stent thrombosis, these variables did not reach statistical significance.

The timing of stent thrombosis was acute in 1/23 patient, subacute in 20/23 patients and late in 2/23 patients. In both cases of late stent thrombosis, a bare metal stent had been used. One of the patients only used oral anticoagulants and suffered from a stent thrombosis after 166 days. The second patient with a late stent thrombosis after 80 days initially underwent a PCI of a diffusely diseased LAD. The PCI was technically difficult and resulted in stent underexpansion and a sidebranch event (dissection of diagonal). Antiplatelet therapy was used as prescribed.

With regard to the reason for stent thrombosis, two cases could be explained by incorrect use of antiplatelet agents. An 80 yrs old patient did not use any anti-platelet drugs at home besides insulin and suffered from a stent thrombosis after 10 days. The other patient only used oral anticoagulants and did not use the aspirin and clopidogrel that were prescribed. In 8 cases, a technical reason was identified. In one patient both stent underexpansion and dissection of a sidebranch were detected. Three patients regarded stent underexpansion only, 1 patient had a sidebranch event only and 2 patients had an unrecognized dissection at the stent edge. The last patient concerned a primary PCI in a

patient with an anterior wall infarction. This case was particularly complex because of a diffusely diseased LAD and incessant ventricular fibrillation. This resulted in a difficult and prolonged PCI procedure in which a residual stenosis of > 50% was accepted. In the remaining 13 patients, no technical comments could be made.

Table 2.

	No stent thrombosis (n=1286)	**Stent thrombosis (n=23)**	**P value**
Age (years)	62±12	67±11	0.047
Male sex	0.73	0.83	ns
Indication			
-Stable angina pectoris	0.49	0.48	0.000
-NTSE=ACS	0.23	0.26	ns
-STE-ACS	0.26	0.26	0.000
Multivessel PCI	0.13	0.13	0.009
Current smoking	0.60	0.75	ns
Hypercholesterolaemia	0.50	0.37	ns
Hypertension	0.46	0.42	ns
Diabetes	0.18	0.25	ns
Positive family history	0.47	0.53	ns
Renal dysfunction	0.14	0.29	ns
Previous MI	0.26	0.35	ns
Previous PCI	0.25	0.30	ns
Previous CABG	0.06	0.04	ns
Good LV function	0.78	0.50	ns
Procedural characteristics			
Segments, no.	1658	23	
Vessel			
- Left main	0.01	0.0	ns
- Left anterior descending	0.41	0.70	0.009
- Right circumflex	0.23	0.09	ns
- Right anterior descending	0.33	0.22	ns
Graft	0.02	0.0	ns
Lesion characteristics			
- Type A/B1	0.43	0.35	ns
- Type B2/C	0.57	0.65	ns
TIM1 3 flow	0.70	0.78	ns
Thrombus	0.25	0.22	ns
GP IIb/IIIa-I	0.23	0.17	ns
Stent thrombosis	0.23	0.13	ns

NTSE-ACS=unstable angina, STE-ACS=acute myocardial infarction, MI=myocardial infarction, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft, LV=left ventricle.

DISCUSSION

In this unselected cohort of 1309 consecutive patients undergoing stent implantation, a 1.8% cumulative incidence of stent thrombosis was noted. There were no differences between the DES and BMS group (1.4 and 1.9% resp). The incidence is higher than the reported incidence of stent thrombosis of 0.4% at 1 year for sirolimus, and 0.6% at 9 months for paclitaxel in major clinical trials[5-7]. However, it appears to be comparable to registries and observational cohort trials that more closely reflect real world patients. For example, Iakovou *et al.* [9] conducted a prospective multi-center study to evaluate the incidence, predictors and outcome of stent thrombosis after implantation of drug-eluting stents in routine daily practice and reported an incidence of 1.3% at 9 months.

Of interest is the fact that we could not demonstrate a difference between BMS and DES. A comparison is difficult to make because DES were used in specific patient categories that were considered to be prone to in-stent restenosis (such as diabetes, in-stent restenosis, long lesions and small vessel diameter). This selection has biased this study. On the other hand, it reflects the daily practice and is applied in most budget-limited centers. Despite differences in baseline characteristics, it is at least remarkable that there were no differences in stent thrombosis rates because DES were used in more complex and longer lesions.

The majority of the cases with stent thrombosis occurred within a month. Only 2/23 cases presented as late stent thrombosis. Both cases were initially treated with bare metal stents. Although it is well known that late stent thrombosis can occur in DES, it should be emphasized that BMS can also be involved in late stent thrombosis.

In 2/23 patients with stent thrombosis there was an apparent relation with incorrect use of antiplatelet agents. This is in accordance with other studies that have demonstrated that withdrawal of anti-platelet agents is associated with a 90-fold increase in risk of stent thrombosis[9]. It is therefore of utmost importance that patients who receive a stent are well informed and receive proper instructions about medication use. In one third of the cases we could identify certain technical flaws. Dissection at the edges of the stent, stent underexpansion and sidebranch events are well-known risk factors for stent

thrombosis and may have predisposed to stent thrombosis in these patients. In more than half of the patients we had no explanation for the occurrence of stent thrombosis. In these patients, an uneventful PCI was performed in combination with correct use of anti-platelet therapy. We speculate that these patients may be resistant to the antiplatelet effects of aspirin and clopidogrel[10]. Variability between patients to platelet inhibition is well known. Up to 10% of patients treated with clopidogrel are resistant to its effects and as many as 25% are only partially responsive[11]. Muller *et al.*[11] evaluated platelet inhibition in a group of patients undergoing elective PCI, and demonstrated that among the group of non-responders there were two incidents of subacute stent thrombosis after PCI. Also several other studies have demonstrated an association between resistance to antiplatelet drugs and clinical outcome[12]. Future research is needed to evaluate the role of antiplatelet resistance to aspirin and clopidogrel in the occurrence of stent thrombosis.

There are several limitations of this study. The number of stent thrombosis is low which has an important impact on the statistical power of our analysis. Second, a follow-up period of 9 months is relatively short. It is feasible that the incidence of stent thrombosis at the long term may be higher. Data are scarce because most trials have a follow-up time of 9 to 12 months. Recent data from the Basket-Late trial, evaluating DES vs. BMS at 18 months in real-world patients, did not show differences in primary endpoints death / myocardial infarction but event rates of 8% were reported[13]. In addition, a recent meta-analysis by E Camenzind[14], concerning all available data of the randomized double-blind clinical trials comparing 1st generation-DES to the respective BMS control, reported a higher incidence of death and myocardial infarctions in the DES group. Because of these concerns, a FDA Circulatory System Devices Panel gathered on December 7th 2006. They recommended several strategies to improve the quality and usefulness of research on stents, including large registries with matched controls, more randomized trials comparing DES to outcomes with BMS, coronary artery bypass grafts or medical therapies. A few months later an entire issue of the new England Journal of Medicine was dedicated to this topic with 5 original articles about stent thrombosis and DES. There were 4 meta-analyses by different groups evaluating the safety of both sirolimus- and paclitaxel-eluting stents as compared to bare metal stents [15 – 18]. Although there was

a lower number of revascularization procedures in the DES group, no differences in mortality and myocardial infarctions could be demonstrated. Although the studies were underpowered, there was a tendency to a higher rate of stent thrombosis in the DES group. New data were provided by a large Swedish registry comprising 19.771 patients who underwent a PCI in 2003 or 2004 [19]. Interestingly, up tot 6 months a lower event-rate was noted in the DES group which can be translated into less in-stent restenosis and less re-interventions. However, after the first 6 months, a higher event rate was noted in the DES group and at 3 years, mortality was 18% higher in the patients treated with DES. It is obvious that we need large randomized trials to evaluate the long-term safety of drug-eluting stents and determine the optimum duration and dose of dual-anti-platelet therapy. Until these questions are answered, a more restrictive use of DES seems advisable with attention for the current 'on label' indications approved by the FDA.

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One Year Results of a new in situ length-adjustable stent platform with a biodegradable Biolimus A9 eluting polymer: Results of the CUSTOM-II trial.

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ABSTRACT AND KEYWORDS

Aim To assess the safety and efficacy of the XTENT® customizable drug-eluting stent system in the treatment of patients with single long or multiple coronary lesions referred for PCI.

Methods and Results

The CUSTOM-II Trial enrolled 100 patients with *de novo* lesions in native coronary arteries presenting with either single long lesions (n=69) of ≥ 20 mm length or up to two lesions with a total cumulative anticipated stent length of 60 mm of stent (n=31). Patients were assessed angiographically at 6 months, and clinically at 1 year.

Of the 100 patients enrolled, 9 patients experienced a MACE, including five patients whose MACE occurred during index hospitalization (2 NonQ-MI, 2 Q-MI and 1 probable stent thrombosis-related death), and four target lesion revascularizations (TLR) at 6 months. No MACE or stent thrombosis was reported between 6 and 12 months follow-up. In-segment late loss at 6-months was 0.22 ± 0.28 mm, and in-stent late loss had a range of 0.31 ± 0.31 mm.

Conclusion

The XTENT® customizable stent is clinically safe and efficacious as judged by angiographic and clinical variables through 12 months follow-up. Further follow-up and larger randomized comparative studies are needed for its clinical positioning.

Keywords: drug-eluting stents, restenosis, stent thrombosis, degradable polymer, Biolimus A9

INTRODUCTION

Drug-eluting stents (DES) are the current standard of care for the percutaneous treatment of coronary artery disease. Recently, there have been concerns regarding the occurrence of late stent thrombosis in the first generation of DES. In these stents, the drug carrier consists of a durable polymer that remains intact even after the drug is completely eluted and this in turn could elicit a chronic inflammatory response, delayed healing and (very-) late stent thrombosis.[1-6]

Fully biodegradable polymers on the next generation of DES should degrade following drug delivery and leave behind only a bare metal stent, thus potentially reducing the rate of stent thrombosis. The combination of the polylactic acid (PLA) carrier and the Biolimus A9 drug has shown promising results in both the prevention of clinically-driven target lesion revascularization (TLR) and the reduction of stent thrombosis. [7,8]

Although first generation DES have brought significant advances to the field of interventional cardiology, current stent designs and methods of delivery can limit their effectiveness especially during the treatment of long and multiple coronary lesions. This procedure is complex and often results in suboptimal angiographic results and increased radiation exposure to both the physician and to the patient. Furthermore, multiple delivery systems and stents that are being used result in increased costs for healthcare providers.

The XTENT® Custom-NX Catheter System (Xtent Inc, USA) allows for *in situ* customizable implantation of balloon-expandable stents of up to 60 mm. The system enables the physician to adjust the stent length to the appropriate length of lesion to be treated within the coronary artery. This *in situ* customization occurs in the same procedural setting as the stent implantation and does not require the physician to predetermine the stent length. Additionally, due to the unique design of the XTENT® Custom-NX System, the risk of inappropriate lesion coverage and stent overlap is eliminated.

METHODS

Patients

Patients were enrolled at 10 centres across 4 countries (see Appendix for all participating study sites). The study protocol was approved by the institutional ethics committees, all patients provided written informed consent, and the study complied with the European-recognized Standard ISO-14155 and the Declaration of Helsinki. Those eligible for balloon angioplasty with symptomatic ischemic heart disease, characterized by *de novo* coronary artery lesions in reference vessel diameters from 2.5 mm - 3.0 mm were included in this study, provided all inclusion criteria were met. The main criteria included *de* novo coronary lesions (no internal mammary or saphenous vein grafts) in two main categories: Either single, long lesions ≥ 20 mm in length or multiple lesions with a cumulative lesion length needing a maximum of 60 mm of stent. Of the multiple lesion cohort, up to two lesions could be treated. *Table 1* summarises the main inclusion and exclusion criteria.

Table 1 Main inclusion/exclusion criteria

Inclusion criteria
• Clinical evidence of ischemic heart disease or a positive functional study. • *De novo* target lesion stenosis >50% and <100%. • Distal and proximal reference vessel diameters ≥2.6 mm and <3.1 mm. • Cumulative lesion length treatable with a maximum of 60 mm of stent length. • Lesion length ≥20 mm in case of 1 lesion to be treated. • In case of 2 treatable lesions, each lesion had to be located within the same coronary tree. • Target lesion in native coronary artery (no internal mammary or saphenous vein grafts).
Exclusion criteria
• Left ventricular ejection fraction <30%. • Evidence of an acute myocardial within 72 hours of the intended treatment. • Pregnancy or woman of childbearing potential without adequate contraception. • Need for device or procedure other than PTCA (e.g. directional coronary atherectomy, excimer laser, rotational atherectomy). • Previous stenting in the target vessel. • Evidence of thrombus in target vessel or excessive tortuosity (2 bends >90° to reach the target lesion). • Significant stenosis (>50%) proximal or distal to the target lesion that may require revascularization or impede run off. • LAD disease with obstruction >50%. • Location of target lesion at the ostium of the LAD, RCA or circumflex vessel. • Involvement of a side branch >2.0 mm in diameter.

Abbreviations: CABG=coronary artery bypass grafting; DES=drug-deluting stent; LAD=left anterior descending artery RCA= right coronary artery

Device Description

The XTENT® Custom-NX 60 DES system is comprised of multiple stent segments and an integrated balloon-inflatable delivery system, allowing for the treatment of reference vessel diameters of 2.5 mm to 3.0 mm. The system comes in 3 different sizes (2.5 - 3.0 - 3.5 mm) but for this study only the 3.0 mm device was available and used. The stent is balloon expandable and protected by an outer sheath. Each stent segment is 6 mm in length with a total of 10 segments. The segments have an interdigitated design that permits excellent scaffolding between segments upon balloon inflation. Each single stent segment is composed of a cobalt chromium mesh frame, a primer layer of inert material (parylene C) and the drug-eluting coating formulation. By manipulating the components of the delivery system, the operator can control the number of stent segments to be deployed *in situ*, allowing for a customized stent length to match the lesion length. The semi-compliant delivery balloon of the device allows for achievement of up to 0.5 mm difference in stent diameter at the same coronary segment, therefore the distal tapering in the treatment of a long lesion has not been a clinical issue. The delivery system of the device is illustrated in Figure 1. The drug-eluting coating formulation used in the Custom NX DES System combines the Biolimus A9 drug (93.6 mg/segment) together with polylactic acid (PLA) coating. Biolimus is modified at position 40 of the rapamycin ring to enhance its lipophilicity and elution rate. The rapamycin ring structure binds to an intracellular receptor, the FK506 binding protein (FKBP-12), forming the macrolide/FKBP-12 complex that subsequently binds to mTOR (mammalian target of rapamycin). By this means, Biolimus interrupts intimal cell migration and proliferation by arresting the cell cycle in the late G1 phase. In addition, the presence of asymmetric PLA polymer coating on the study stent presents an advantage over durable polymers, eliminating a possible chronic source for inflammatory reactions and thrombosis after the drug has eluted, as was mentioned above. The PLA carrier used is completely absorbed by approximately 12 months, leaving only the bare metal stent and thereby reducing the risk of any late adverse events. PLA has a controlled biodegradable profile, degrading first into lactic acid, a natural metabolite, and finally into carbon dioxide and water.[9,10]

Device implantation:

Subjects meeting the eligibility criteria underwent physical examination and ECG testing. Baseline angiography of the target vessel was performed and the estimated length of the target lesion was determined as well as other angiographic characteristics of the target lesion, including morphology and classification. The guiding catheter used during the procedure had a minimum internal diameter of ≥6 French. Prior to treating the target lesion, standard percutaneous transluminal balloon angioplasty was performed to pre-dilate the stenotic area at the discretion of the operator. Following the placement of a standard guidewire, the XTENT® Custom-NX system was delivered to the site of the target lesion. Opaque markers on the balloon inflation lumen and the protective sheath allowed for accurate positioning of the catheter. Features of the device's handle enabled the operator to control the number of stent segments to be deployed and also to separate the exposed stent segments from those remaining protected under the sheath of the catheter. If desired, for better stent apposition, the operator modified the length, repositioned and re-inflated the balloon *in situ*. For those in the multiple lesion cohort, the XTENT® Custom-NX DES system was reset and used to treat the additional lesion with the remaining stent segments. An example of a patient with two long coronary lesions in RCA that was treated with the XTENT® Custom-NX DES system, is shown in Figures 2-6. Prior to the index procedure, at least 75 mg of aspirin QD for at least seven days prior to the procedure and 300 mg clopidogrel or 500 mg ticlopidine per os were given. During the procedure, heparin was given by IV per hospital protocol. Intracoronary nitroglycerin 50-200 µg bolus was given prior to baseline angiography and post-intervention Two or more orthogonal views were taken to show non-foreshortened views of the target lesion. Quantitative coronary angiographic and IVUS endpoints were assessed after PCI and at six months included binary restenosis, late loss, loss index, late absolute minimal luminal diameter (MLD) and minimal lumen area (MLA). Post-procedure, 75 mg clopidogrel or 250 mg ticlopidine were recommended daily for a minimum of 90 days post-stent implantation.

Study Endpoints - Primary Endpoint

The primary endpoint for this study was the rate of Major Adverse Cardiac Event (MACE) at 6 months. MACE was defined as cardiac-related death, any myocardial infarction, and clinically-driven target lesion revascularization. Q-wave MI was defined as the development of new, pathological Q waves in 2 or more contiguous ECG leads (as assessed by the ECG core laboratory) with post-procedure CK or CK-MB levels elevated above normal. Non-Q-Wave MI was defined as elevation of post-procedure CK levels > 2.0 times normal with elevated CK-MB in the absence of new pathological Q waves (WHO definition).

Secondary Endpoints

Secondary endpoints for this study included angiographic endpoints, device performance endpoints and other safety endpoints. Performance endpoints included procedural success, defined as the achievement of a final diameter stenosis of <15% (visual estimate) without an occurrence of MACE during the hospital stay. Successful device performance was defined as the successful delivery and deployment of a customized stent to the target lesion covering the total lesion length and achieving a final diameter stenosis of <15% by visual estimate.

Secondary safety endpoints include MACE rate at 30 days and 12 months, the incidence of bleeding and/or vascular complications, the incidence of (sub)acute stent thrombosis (SAT) at 30 days and stent thrombosis at 12 months. Stent thrombosis definition was revised during the course of the trial to adopt the newly recommended ARC definitions[11]. All events were therefore reviewed and adjudicated by an independent clinical events committee per those definitions. All patients in both trials underwent clinical follow-up at 30 days, 6 and 12 months and subsequently will undergo clinical follow-up annually for 5 years. All data points were monitored by an independent monitoring CRO and all events were adjudicated by an independent Clinical Event Committee.

QCA & IVUS

Quantitative Coronary Angiography analysis and Intravascular Ultrasound analysis were performed by two independent core laboratories. (See appendix). In three patients an OCT study was performed at follow up, showing excellent results with minimal neointimal formation and no signs of late malapposition.

Statistics

Categorical variables were summarized using counts and percentages. Continuous variables were summarized using mean, standard deviation, minimum value, maximum value, and median. Rate of MACE at twelve months is presented with a 95% confidence interval and in hierarchical manner. All safety data are summarized as part of intent to treat analysis.

RESULTS

The CUSTOM II trial enrolled 100 patients, using the XTENT® Custom-NX DES system and enrollment was completed in October 2006 at 10 cardiology centers in Europe. Two cohort groups represented single long lesions treated (n=69) and multiple lesions (n=31). The mean age of the population was 64.2 years. 77% were men and 26% were diabetics, 72.4% had a history of hyperlipidemia, 65.7% hypertension, 36% were previously revascularized (PCI or CABG) and 16% presented with a history of myocardial infarction. Lesion characteristics demonstrated more complex morphology as 65.1% were B2/C grade lesions according to the ACC/AHA classification.

Patient and lesion characteristics in the CUSTOM-II trial are summarized in Tables 2 and 3. Mean lesion length was 28.7 mm with a mean stent length implanted of 37.9 mm, representing the ‘ real world ‘ difficult lesion subset. The distribution of the stent length for the single long lesion cohort (n-69) is provided in Figure 9. For each length group represented one may deduct the number of used segments in the system in order to calculate the discarded segments. In the multiple lesions cohort , half of the patients

were treated with one Custom-NX system. The rest of them were treated with the use of 2 devices. A second device was utilized when crossing from one coronary tree to another where rewiring was necessitated, because at the time of enrollment the device was not validated to be removed from the circulatory system of the patient and then reinserted. In several patients also a second device was utilized because of inadequate lesion length coverage with a single device.

Table 2. Patient characteristics (n=100 patients)

Charasteristic	**Patients with Long Lesions (n = 69)**	**Patients with 2 lesions (n = 31)**	**All patients (n = 100)**
Age (years)	63.7±10.2	65.4±9.5	64,2±10
Male sex (%)	75.4	80.6	77
Smoker (%)	49.3	45.2	48
Hyperlipidaemia (%)	75.0	66.7	72.4
Hypertension(%)	62.3	73.3	65.7
Diabetes mellitus (%)	24.6	29	26
Prior PCI(%)	31.9	29	31
Prior CABG(%)	4.3	6.5	5
Prior MI (%)	17.4	12.9	16
Family History of CAD (%)	41.7	58.1	47.3
Peripheral Vascular Disease	17.6	6.5	14.1

Abbreviations: CABG=coronary artery bypass grafting; CAD=coronary artery disease; PCI=percutaneous coronary intervention; SD=standard deviation

Table 3. CUSTOM II: Lesion characteristics (*n* = 100 patients)

Characteristic	**Patients with Long Lesions (n = 69)**	**Patients with 2 lesions (n = 31)**	**All patients (n = 100)**
Lesion Characteristics			
- RCA (%)	42.4%	42.9%	42.9%
- LAD (%)	38.8%	35.7%	37.2%
- CX (%)	18.8%	21.4%	19.9%
ACC/AHA Grade:			
- A (%)	1.4%	9.4%	5.4%
- B1 (%)	23.2%	32.8%	29.5%
- B2 (%)	31.9%	42.2%	38.0%
- C (%)	36.2%	15.6%	27.1%
Reference vessel diameter [mm (mean ± SD)]	2.61 ± 0.42	2.52 ± 0.48	2.57 ± 0.45
Lesion Length [mm (mean ± SD)]	31.7 ± 12.6	25.2 ± 14.9	28.7 ± 14.0
Stent Length [mm (mean ± SD)]	44.2 ± 12.1	30.5 ± 13.8	37.9 ± 16.2
% Diameter Stenosis (mean ± SD)	66.2 ± 15.0	63.2 ± 12.7	64.8 ± 14.1

Abbreviations: ACC/AHA=American College of Cardiology/American Heart Association; LAD=left anterior descending artery; LCX=left circumflex artery fraction; RCA=right coronary artery;SD=standard deviation

Clinical follow-up at one year was completed in the entire cohort (100% of patients) and is reported in Table 4. Ninety days of dual antiplatelet therapy was recommended per protocol to patients that were enrolled in the CUSTOM-II study. At one month follow-up ninety seven (98%) patients were receiving dual therapy, aspirin and clopidogrel. At six month follow up ninety one (92%) patients were receiving dual antiplatelet therapy. 70% of all patients were taking clopidogrel at 12 month follow up. Procedural success was achieved in 98% of the cases and there were no device-related complications. There was one hospital death 48-hours post procedure, prior to hospital discharge, in a patient treated with a single long lesion, adjudicated as a probable stent thrombosis according to ARC definition. No other cases of stent thrombosis were recorded up to one year follow-up. There were 4 cases of non-fatal myocardial infarction during the index hospitalization identified in patients with lesions greater than 25mm. Four cases of clinically driven

TLR were reported during the first 6 months follow-up, while there were no new events between 6 and 12 months after the procedure. Overall MACE rate at 1 year remained at 9%. At 6 six months clinical follow up was completed for all patients (100%) and angiographic follow-up was performed in 90% of the patients. Follow up QCA and IVUS results are reported in Table 5. In-stent late loss was 0.31± 0.31 mm and in-segment late loss was 0.22 ± 0.28 mm. Patients will be followed annually for 5 years.

Table 4. Clinical outcomes 1 year after the procedure (*n* = 100 patients)

TOTAL LESIONS	**LESION LENGTHS (mm)**					**LONG LESIONS N=47**		
	< 15mm	15-20mm	20-25mm	> 25mm	All Lesions	>25-30	>30-35	>35
Lesions N=114	18.4%	9.6%	12.3%	59.6%	100.0%	19.3%	14.9%	25.4%
Cardiac Death				1*	1*			1*
MI				4	4	3		1
QWMI				2	2	2		
NQWMI				2	2	1		1
TLR		1	1	2	4	1		1
Total MACE	0	1	1	7	**9**	4	0	3
Late Stent Thrombosis	0	0	0	0	0			
Binary Restenosis		0	1	7	8	1	2	4

*In hospital death 48 hours post procedure prior to hospital discharge

Table 5. Postprocedural and 6-month angiographic results of 106 lesions in 90 patients.

Charasteristic	**Post PCI**	**6-month follow-up**
Minmal lumen diameter [mm (mean ± SD)]	2.33 ± 0.32	2.03 ± 0.42
% Diameter Stenosis	14.9 ± 6.9	21.6 ± 13.3
In Stent Late Loss [mm (mean ± SD)]	-	0.31 ± 0.31
In Segment Late Loss [mm (mean ± SD)]	-	0.22 ± 0.28
Late Loss Index (mean ± SD)	-	0.23 ± 0.22
Binary Restenosis (%)	-	7.5
Minimal lumen area [mm^2 (mean ± SD)]	5.0 ± 1.1	4.9 ± 1.4

SD=standard deviation

DISCUSSION

The results of the CUSTOM II trial confirm that the XTENT® Custom NX stent is highly deliverable and appears safe and efficacious as judged by angiographic and clinical variables at 12 months follow-up both in single long, or multiple lesions. While most new stent platforms have been studied in predominantly simple lesions,[12-14] CUSTOM II involved more "real-world" anatomical characteristics consisting of very long or multiple lesions.

Regarding in-stent late loss, the results of the biolimus-coated XTENT® Custom-NX compare favorably with those of sirolimus-eluting stents (late loss up to 0.20 mm)[14-16] and paclitaxel-eluting stents (late loss 0.30-0.49 mm).[7,17] This efficacy is accompanied by an excellent safety profile with an overall MACE rate of 9%. Remarkably, no late stent thrombosis was reported between 6 and 12-month follow-up, although only 70% of all patients were taking dual antiplatelet therapy at 12 month follow up. In addition to the Biolimus A9 drug, the presence of the biodegradable PLA polymer seems to be an advantage compared to the durable polymers used in the first-generation DES, potentially contributing to the low incidence of stent thrombosis.

In a recent randomized comparison of a DES platform using Biolimus-A9 with PLA coating versus Taxus Liberté®, the biolimus-eluting stent was found to be superior to the paclitaxel-eluting stent (PES) in terms of late loss at 9 months (0.15±0.27 for BES vs. 0.32±0.33 for PES, p=0.006). Clinically-driven target lesion revascularization was 0% in the biolimus group versus 2.9% in the PES group.[7] The neointimal suppression induced by the Biolimus A9 / PLA drug combination as demonstrated in CUSTOM-II, appears superior not only to paclitaxel but also to zotarolimus (ZES) and additionally resembles the suppression previously reported for sirolimus[14-16] and everolimus-eluting stents (EES):[13,18] In detail, in the SPIRIT–II trial, six months in-stent late loss with EES for lesions <28mm was 0.11±0.27mm.[13] In the ENDEAVOR-II trial, in-stent late loss for the ZES group was 0.67±0.46 mm [12].In a large trial that compared PES and SES in long lesions, 6 month in-stent late loss was 0.45±0.55 mm and 0.09±0.37 mm respectively (p<0.001 in favour to sirolimus-eluting stents).[17] More data is needed regarding the treatment of long lesions with the newer zotarolimus and everolimus stents.

These favorable results of the CUSTOM-II trial confirm the clinical and angiographic benefits of the Biolimus A9/PLA formulation, while extending them in a patient population with very long and multiple coronary lesions. Although both lesion and stent lengths in the CUSTOM-II trial are much longer than in previously reported studies with a relatively smaller reference vessel diameter, there was no evidence of increased MACE or target vessel failure (TVF) with the use of long-stented segments. In an indirect comparison of the CUSTOM-II trial primary endpoint to the 9-month results from TAXUS-V and VI trials that also involved long coronary lesions, MACE rates after XTENT® DES implantation were much lower than those reported with Paclitaxel-eluting stents (e.g. 9% vs. 20.4% vs. 16.4% respectively), although mean lesion length treated was longer (28 vs. 25 vs. 20.9 mm respectively).[19,20] Another positive finding was that these favorable outcomes in CUSTOM-II are noticed even in relatively small vessel diameters, again compared to TAXUS-V and VI (2.57 mm in CUSTOM-II vs. 2.65 / 2.82 mm respectively).[19,20] In a recent study in which extensive DES coverage of coronary lesions was performed, (defined as >50 mm stent length), 6-month TLR was found to be 6.7% and MACE plus TLR was 13%. Further analysis showed that stent length was the only independent predictor of MACE plus TLR.[21] In CUSTOM II, 1-year TLR in the XTENT® DES group was 4% and MACE was 9%; these rates are favorable compared to those mentioned in trials testing other DES platforms in long lesions.

Theoretically, this new stent platform offers some major advantages over contemporary practice. First, the current practice of stent length estimation from fluoroscopy is avoided by virtue of *in situ* customization coupled with the ability to cover the entire lesion length (up to 60 mm), which is longer than all currently available DES stents. This reduces the risk for geographical and longitudinal miss, events which can occur with procedures involving complex and diffuse lesions, where the dilated coronary segments are often not adequately covered by multiple fixed-length stents. Next is the potential to avoid stent overlap, which has been proven to be an independent risk factor for MACE[22]. Medial necrosis, increased intimal growth, and in some cases adventitial inflammation, have been reported at the site of DES implantation, especially using paclitaxel-eluting stents [1,5,23] This increases the risk of stent thrombosis at sites of DES overlap, given that drug and/

or polymer concentrations are significantly higher in the overlapped segments.[2,22,25,26] Furthermore, the rate of peri-procedural myonecrosis in the TAXUS-V trial was found to be significantly higher in the subgroup of patients who received overlapping PES versus the control group (8.3% vs. 3.3% respectively - p=0.047), because of the compromised blood flow at the side branches which increases proportionally if multiple/overlapping stents are applied.[20] Approximately 33-35% of patients enrolled in the SIRIUS and E-SIRIUS trials were treated with overlapping stents and an estimated 29% in TAXUS VI.[13,19,27] The unique features of the XTENT® Custom-NX DES system minimize the risk of inappropriate or inadequate lesion coverage and eliminate the need to use multiple or overlapping stents.

Apart from avoiding stent-overlap, another major advantage of the XTENT® Custom-NX system is the avoidance of stent fracture due to the unique stent design. Stent fracture is likely to be affected by mechanical stress provoked by rigid structures. In a recent study in which 280 patients were treated solely with sirolimus-eluting stents, the incidence of stent fracture was 2.9% while in-stent binary restenosis and clinical TLR rates were very high in those patients that had stent fracture (37.5% and 50% respectively).[28] In another study using SES, stent fracture was identified as a cause of in-stent restenosis in 10 out of 26 in-stent restenosis lesions (39%).[29] Its predisposing factors may be vessel tortuosity and use of overlapping stents.[29,30]

Finally, the benefits of the XTENT® Custom-NX system will lead to reduced procedural times, resulting in diminished contrast dye administration, increased patient safety, and lowered costs, since multiple stent length devices and balloon catheters on stock could be avoided.

The favourable results of the 1 year follow-up of the CUSTOM II study, in a high-risk patient population with complex multi-vessel coronary artery disease, of whom 35% were diabetics, confirm the safety and all potential theoretical benefits of the XTENT® Custom-NX system. These long-term results also demonstrate the safety of *in situ* customization to treat complex coronary lesions with a single catheter insertion and confirm the superior efficacy of the Biolimus-A9 drug with PLA biodegradable coating stent formulation.

Conflict of Interest

Prof. Grube is consultant to Xtentinc

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APPENDICES

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10

Registry on a new T technique for bifurcation coronary lesions: the Utrech-"T"-experience.

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INTRODUCTION

Bifurcation lesions occur in more than 20% of coronary angioplasty interventions.[1] Percutaneous treatment of coronary bifurcation lesions, pose a number of technical challenges to the interventional cardiologist. Each lesion has to be approached with its own, targeted solution in the context of the clinical picture, anatomy, and pathology. A number of established techniques are available, in order to achieve acceptable clinical outcomes. Although the most common approach is the provisional stenting of the side branch, various techniques that use two stents have been described and include the simultaneous 'kissing stent' technique, as well as approaches in which there is sequential placement of the stents ('Y','T', "crush", 'V', and the 'culottes' technique). Novel 'bifurcate' stent designs are developed to allow complete coverage with a single stent of both branches but their testing is in a preliminary stage. Furthermore, difficulties in anatomy combined with reduced deliverability, still inhibit the widespread use of these dedicated devices.

In this report we describe our experience with a new approach for the treatment of bifurcation lesions with a new simplified technique that involves the sequential positioning of two stents, first in the side branch (SB) and second in the main branch (MB). The main aim of this technique is to provide a complete coverage of the bifurcation lesion and of the carina with a relatively small portion of the main branch, only distally to the bifurcation, being scaffolded with a triple layer of stent. As a result, this procedure can be characterized as "a modified T stenting technique with minimal crush". We report the clinical outcomes in the cohort of patients in which we have performed it.

METHODS

Description of the technique

Our technique is a new T stenting approach that briefly can be described as follows (Figures 1-3): After the predilatation of the bifurcation, two wires are inserted in both

branches of the bifurcation lesion. Then a stent in the side-branch and a balloon in the main branch are advanced at the site of bifurcation. In order to ensure adequate scaffolding of the side branch ostium, the side branch stent is slightly pulled back, so that a small portion of the distal part of its proximal end is deployed inside the main branch. The stent is then correctly positioned at the side branch ostium, "cushioned" against the balloon in the main branch during a low inflation of the MB balloon (~ 4 Atm.), followed by side branch stent deployment at about 16 Atm. Thereafter a sequential high-pressure inflation of the side and of the main branch is performed with these two balloons, in order to create a small detachment of the side branch stent struts and to create a wide opening towards the side branch. This should provide complete coverage of the side branch ostium, leaving no gaps. After complete removal of the side branch delivery system (included the wire), a stent is positioned in the main branch and deployed with high pressure, resulting in a small crush of the proximal part of the side branch stent [only at the distal carina, (Figure 3)]. It is important to stress here that this technique does not necessitate a final kissing balloon dilatation in order to open the struts of the main branch stent, to facilitate the crossing towards the side branch. Therefore no recrossing to the side branch and final "kissing balloon" techniques were performed. This approach is completely different from previous described "modified T" techniques because of the double but sequential SB / MB stenting without post-stent dilatation procedures.

All patients were pretreated with aspirin and clopidogrel. A 300 mg loading dose of clopidogrel before the index procedure was administered, if patients were not pretreated. Initially all patients received intravenous unfractionated heparin (70 IU/kg). Administration of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Every patient was on maintenance aspirin therapy and clopidogrel was administered for 12 months following DES implantation and for 6 months following bare-metal stents (BMS) implantation.

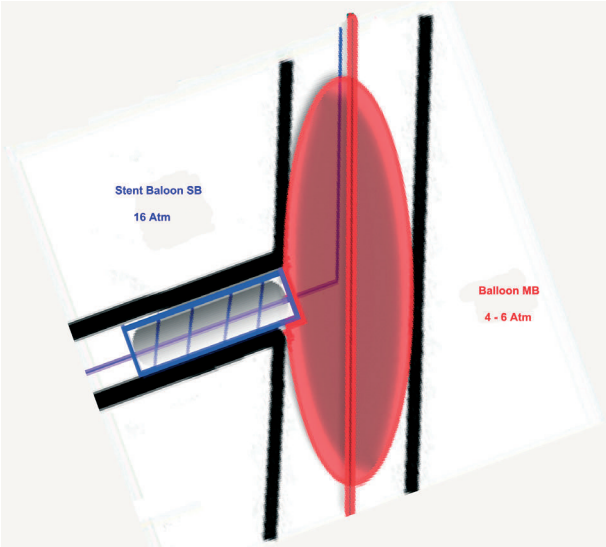

Figure 1. A stent is positioned in the side branch "cushioned" against a balloon being in the same time positioned at the main branch and inflated at low (4-6) Atm, followed by stent deployment at about 16 Atm. Following sequential inflations in the side – main branch, complete coverage with stent struts of the side branch is achieved, leaving no gaps.

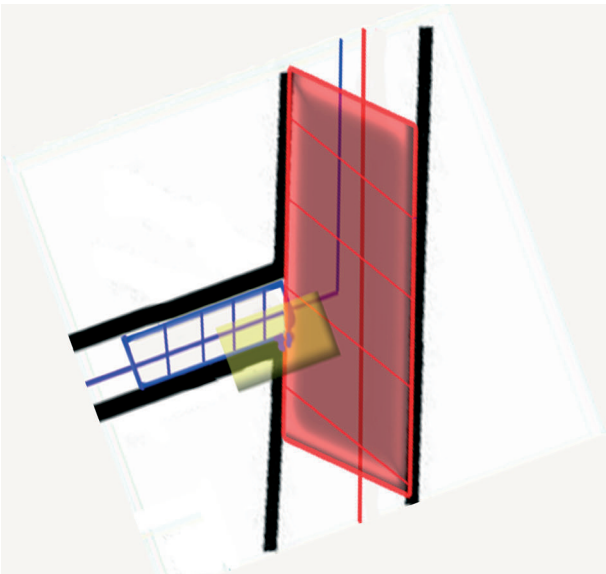

Figure 2. After complete removal of the side branch delivery system, main branch stent deployment at high pressure follows.

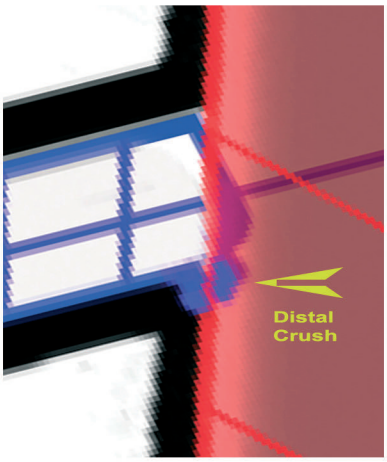

Figure 3. Magnification of the area of "crushing": A small portion of the proximal part of the side branch stent at the distal carina is deployed and "crushed" inside the main branch (minimal distal crush).

Appendices

DES: drug-eluting stents

BMS: bare-metal stents

LAD: Left Anterior Descending artery

LCX: Left Circumflex artery

TVR: Target Vessel Revascularisation

Study population

Patients with lesions involving a bifurcation lesion with a side branch equal or more than 2.0 mm in diameter, were considered eligible for the study. The angle between main and side branch should be more than 45-50°.

A bifurcation lesion was defined as diameter stenosis > 50% involving the main parent vessel proximal or distal to the origin of a major (>2.0 mm in diameter) side-branch, with or without involvement of side-branch ostium, based on visual assessment on the angiogram. [2]

The clinical characteristics of our patients are summarised in Table 1. 28% of the patient population were diabetics.

Table 1. Baseline Clinical Characteristics

	Population (n=100)
Age, yrs	68
Male, n (%)	92
Current or ex-smoker, n (%)	76
Hypercholesterolemia, n (%)	86
Hypertension, n (%)	70
Diabetes mellitus, n (%)	29
Prior MI, n (%)	38
Prior CABG, n (%)	21
LVEF, %	49
Glycoprotein IIb/IIIa inhibitors, n (%)	55

Values are numbers (%) or mean (SD).

CABG: coronary artery bypass graft surgery; LVEF: left ventricular ejection fraction; MI: myocardial infarction.

Clinical Definitions and Follow-up

Clinical follow-up was performed by telephone contact or office visit throughout the entire follow-up period at one and six months after the index procedure.

Major adverse cardiac events (MACE) at six months follow up was the primary end point of our registry, defined as: cardiac death, myocardial infarction and target vessel revascularization (TVR), either percutaneous or surgical. Q-wave myocardial infarction was diagnosed on the basis of the development of new Q-waves of more than 0.04 sec duration in two or more contiguous leads, with an increase of the creatine kinase level to more than twice the upper limit of the normal range and an elevated MB isoform level. A non-Q-wave AMI was defined as elevation of CK levels >2 times the upper limit of the normal value with an elevated CK-MB level in the absence of pathological Q-waves. TVR was defined as a repeat intervention to treat a luminal stenosis within the stent or in the 5-mm distal and proximal segments adjacent to the stent. Procedural success was defined as angiographic success with TIMI-3 flow both in the main and side branch

without the occurence of death, emergency CABG, repeat PCI of the target vessel, and acute myocardial infraction (AMI) before discharge.

Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel or, (in the absence of angiographic confirmation), AMI in the distribution of the treated vessel not clearly attributable to other causes. According to the timing of the events, three categories of stent thrombosis were specified: intra-procedural, subacute stent thrombosis (from the end of the procedure to 30 days) and late stent thrombosis (>30 days). [3-5]

Statistical Analysis

Continuous variables are presented as mean (SD) or median with interquartile ranges and categorical variables as frequencies (%).

RESULTS

Baseline and procedural characteristics

A total of 100 consecutive patients with suitable bifurcation lesions were treated between November 2004 and December 2005. Baseline lesion characteristics are shown in table 2.

Table 2. Baseline Lesion Characteristics - Lesion Location

Lesion characteristics, n (%)	**Lesions (N=100)**
Lesions type, n (%)	
LAD/Diagonal	40
LCX/OM	29
LM/LAD/LCX	14
RCA/RCA-PL/RCA-PD	17

Values are presented as numbers (%).

LAD = left anterior descending artery; LCX = left circumflex artery; OM = obtuse marginal; PD = posterior descending; PL = posterior lateral; RCA = right coronary artery.

Baseline bifurcation anatomy was classified according to MEDINA classification (table 3). 14% of the lesions were located at the distal left main bifurcation. There was involvement of the main branch in every case that was treated, while the side branch was diseased in 85% of cases.

Table 3. Baseline Bifurcation Anatomy – MEDINA classification*

MEDINA classification type: (Prox. Main branch, dist. Main branch and Side branch involvement)	% of patients
1,1,1	35
1,1,0	15
1,0,1	30
0,1,1	20

* There were not any lesions of the MEDINA types **(1,0,0) - (0,1,0)** and **(0,0,1)** treated.

Quantitative coronary angiography analysis results before and after the procedure are shown in Table 4. Angiographic follow-up was not routinely performed in our patients. IVUS was used in a minority of our cases, according to operator's judgement and in order to assess only the deployment of the main branch stent. Due to a local restrictive policy on the use of DES the majority of patients were treated with a non-DES stent. As a result only 18 patients received sirolimus-eluting stents (Cypher®, Cordis J&J) in both branches, 7 patients received a Cypher® stent at the main vessel and a bare-metal stent at the side branch and 3 patients received a BMS in the main vessel and a Cypher stent in the side branch. Direct stenting was performed in 68% of the side branch lesions.

Table 4. Lesion Characteristics - Quantitative Coronary Angiography Analysis

A. MAIN BRANCH	**Before procedure**	**Post-procedural**
Reference vessel diameter (mm)	2.7 (0.52)	3.31 (0.45)
Minimal lumen diameter (mm)	0.93 (0.51)	2.93 (0.41)
Diameter stenosis (%)	67.4 (16.1)	10.2 (7.7)
Lesion length (mm)	16.0 (9.2)	-

B. SIDE BRANCH	**Before procedure**	**Post-procedural**
Reference vessel diameter (mm)	2.31 (0.48)	2.84 (0.58)
Minimal lumen diameter (mm)	0.81 (0.48)	2.32 (0.44)
Diameter stenosis (%)	63.7 (15.9)	14.9 (9.2)
Lesion length (mm)	10.1 (7.5)	-

Values are presented as numbers (%) - mean (SD).

Clinical Outcomes

Procedural success was noted in all of the cases. Clinical follow-up at 6 months was available in the whole patient population. Clinical outcomes are summarised in Table 5. One 85-year old patient who was treated with 2 BMS in Left Main/LAD/LCX bifurcation, was found dead 4 days after the procedure while at home. Two patients who were treated with 2 BMS suffered a subacute stent thrombosisin the SB and were treated with a repeat PCI without having further complications. The rate of TVR at 6 months was 4%. In detail, there were 2 cases of TVR at the main branch, one in a patient with BMS and one in a patient with Cypher® stent. There were also 2 cases of TVR at the side branch again equally distributed in a patient with a BMS and in a patient with a Cyphe®r stent. There were no TVRs in the group that received a Cypher® stent in the main vessel and a bare-metal stent in the side branch. There was a TVR at the side branch in one out of the 3 patients who received a bare-metal stent in the main vessel and a Cypher® stent in the side branch.

Table 5. Major Adverse Cardiac Events (MACE)

	Incidence (n = 100) (%)
Death	1
Subacute thrombosis	2
TVF by CABG or PCI	4
MACE (total)	7

TVF : Target vessel failure, CABG: coronary artery bypass graft surgery

PCI : Percutaneous Coronary Intervention

DISCUSSION

Even in the current era of drug-eluting stents (DES) and of special dedicated bifurcation stents, the most appropriate method for treating lesions at bifurcations remains to be defined. Follow-up data demonstrates a rather poor clinical outcome, due to recoil and plaque shift at the origin of the side branch. Thus with conventional bifurcation stent

techniques restenosis rates higher than 30% have been reported. In part, all these alternate strategies have developed as no single technique has been found to be superior to the rest. Dedicated bifurcation stent designs are being developed (Invatec Twin rail, Devaxx Acces, Frontier stent TM, SLK-View TM) [6-8]. Their main advantage is that the second lumen of their delivery system is always open and protects the ostium of side-branch during stent deployment, so that additional treatment of the side-branch can be performed optimally. In addition, less metal component and no stent overlap may lead to favorable long-term outcome. Furthermore, there is no destruction of stent struts in the parent vessel. These stents seem to be the more promising treatment for treating bifurcation lesions, but there are also some limitations: i) the deliverability of the currently used dedicated stents is rather limited, especially in cases of difficult anatomy ii) the use of most of these stents increases the duration of the procedure considerably and iii) a great amount of expertise is required to ensure their optimal deployment. As technology proceeds and experience of the operators grows, these problems are likely to be surpassed in the near future.

The emergence of drug-eluting stents offered considerable hope in improvement of outcomes in bifurcations treatment, showing reduction of the incidence of main vessel restenosis and their usage seems to result in lower event rates [9-12]. Until recently though, most of the currently available data regarding the use of DES in bifurcation lesions, are in the form of single center case reports or series, so further evidence-based evaluation is required before a routine use of DES in bifurcation lesions can be finally recommended [13-15]. A recent randomised trial that compared BMS with sirolimus eluting stents showed a better clinical outcome with Cypher®.[16] It is noteworthy that the results regarding side branch restenosis are not encouraging, as the occurence of restenosis at the ostium of side branch remains as high as 21% [12,17-19]. Furthermore, according to a recently published registry that examined the outcomes of DES usage in treating distal left main bifurcation disease, the cumulative incidence of MACE was 30% in an 18 month-period.[20] An arising problem while using DES in bifurcations with current techniques, is the relatively high incidence of stent thrombosis (about 3,5%)[3,5-6,17]. A recent study using crush technique and DES in bifurcations reported an intaprocedural stent thrombosis of 1,7% and a subacute stent thrombosis rate of 2,8% (2% in sirolimus-eluting stents and 4%

in paclitaxel-eluting stents).[12] "Crush" technique may lead to an increased local drug delivery at the proximal part of the parent vessel, with subsequent intense impairment of endothelial function, therefore increasing the risk of thrombosis [21]. Indeed, bifurcation lesions were found to be an independent predictor of DES thrombosis [3]. Prolonged antiplatelet treatment in cases of bifurcations treated with DES seems therefore absolutely necessary, while its optimal duration is not yet known.[14] To reduce the risk of thrombotic events with these techniques, also a more liberal usage of glycoprotein IIb/IIIa inhibitors should be considered.[17] Therefore, because of these unresolved issues regarding the use of DES in bifurcation lesions, as well as a local restrictive policy, we decided to implant BMS (always the new generation chromium-cobalt stents !) in the majority of our patients and not DES. The use of DES was limited to the diabetic subpopulation and avessel diameter less than 2.5 mm in the SB.

Multiple stenting techniques each with their own advantages, indications and problems, have been used to treat bifurcation lesions. [22-24] Stenting of the main vessel only, is currently thought to be the best option even in those lesions in which the diameter of the side branch is >2.5 mm. [19,24-26] Although stenting of the main vessel with provisional stenting of the side branch is the predominant current technique, in many of these procedures the suboptimal final result at the side branch, when this is a large vessel with a sufficient area of distribution necessitates the positioning of a second stent.[27] Also a single-stent strategy should not be applied in most of distal left main bifurcations or in cases of depressed left ventricular function where achievement of complete angiographic outcome is desirable, as well as when the side-branch lesion is too long, calcified and tortuous, making it unlikely that an acceptable result will be obtained with balloon angioplasty only.[28]

In a randomized trial using bare metal stents in bifurcation lesions, comparing single stent with two stents technique, 57% of these cases initially planned to be treated with one stent crossed over to the double-stent group due to unsatisfactory angiographic results! [27] According to our experience, the provisional side branch stenting technique still leads in more than 50% of cases to the final placement of a side branch stent because of suboptimal angiographic results (e.g. dissection, plaque shift and occlusion of a large side branch may occur, resulting in risk of ischemia – and thus persistent angina - of a large

area of the myocardium). When the one-stent technique fails to provide a satisfactory result at the side branch, a "reverse crush" technique follows, that leads to the positioning of a second stent in the side branch, through the struts of the first one. It is obvious that this technique is laborious and can not be recommended as the preferred technique for positioning of two stents in a bifurcation lesion. Furthermore, all techniques that include stenting first of the main branch and a "jailed" wire in the side branch have the potential danger of rupture of the "jailed" wire, especially when using hydrophilic wires. [24,28] Therefore the need for a successful and simplified two-stent bifurcation technique remains and this led us to this new approach.

After an overview of all the current techniques for treating bifurcation lesions, some important issues should be pointed out:

First, the side branch is the weak ring of the chain in terms of higher risk of restenosis. Suboptimal coverage by struts and drugs (in the case of DES) that results in uncovered gaps at the ostium of the side branch, is the major contributing factor to side branch restenosis. In addition to this, plaque shifting from the main branch, as well as extended crushing of the proximal segment of the side branch stent which may result in malapposition and inefficiency of the drug eluting stent (crush technique), also contribute to side branch restenosis.

Second, stent thrombosis is a question when using techniques with a lot of stent overlap at the proximal part of the main branch (crush, culotte), not only in earlier studies but also during the DES era. [5, 6, 24, 29-30]

Third, recrossing the side branch after stent implantation in the main branch either for the positioning of the side branch stent or for final kissing balloon dilatation, is a technically demanding and laborious stage of all the current techniques. It causes an increase of radiation time and of the amount of contrast being used, which are of high importance when treating complex lesions in high risk patients (diabetics, renal impairment). Although use of a final kissing balloon dilatation has shown a favourable effect in the clinical and angiographic outcome when used in crush technique,[12,17] this evidence in favor of final kissing ballon dilatation is not necessarily applied in our technique where the "crushing" of stents is minimal. Furthermore, in a bench study that evaluated DES

platforms while using the provisional stenting technique, the internal crush and the culotte techniques, kissing balloon inflations in crush technique were found to be a cause of stent distortion. It was found that while these inflations expanded the stents well, the stent struts at the distal margin of the ostium were pushed into the main branch. This distortion was not found to be due to the sequence of balloon deflation [30].

We believe that our " T "-approach gives adequate answers to these issues, as it provides – theoretically- full coverage of the ostium of the side branch, leaving no gaps at the side branch vessel ostium. Overlap of stents and crushing at the main branch is minimal, because a very limited portion of the main branch only distally to the bifurcation is being scaffolded with a triple layer of stent. There is no stent overlap elsewhere in the bifurcation, diminishing the risk of thrombosis.

Bifurcation lesions carry a risk of side branch occlusion because of plaque redistribution, the so-called plaque shift across the carina of the bifurcation. Side branch recrossing for final kissing balloon dilatation is not required in our approach so that stretching and deforming of the main stent cells is avoided, thus preserving the geometry of the stent at the main branch. Avoiding final kissing balloon dilatation also makes this technique less technically demanding and time-consuming as it was prevously explained.

The clinical follow up of the patients in our study reaffirms these theoretical advantages of this technique, as we noted a rather low incidence of clinical events after a six months period. In 18% of our patients a drug-eluting stent (Cypher®) was placed and it was a promising finding that both bare-metal as well as sirolimus-eluting stents were rather safe when used according to our approach, although a direct comparison between these two platforms was not the purpose of our registry. Older studies using BMS in bifurcation lesions have shown a rather high incidence of restenosis with TLR rates of about 30%.[26,32] In our study though, the new generation of cobaltium-cromium bare metal stents were used (Driver® -Medtronic, Skylor® -Invatec) in which efficacy data, especially in bifurcation lesions, are lacking. One prospective, multicenter study that evaluated the clinical safety and efficacy of the Driver cobalt-chromium alloy stent in 298 patients with non-bifurcation lesions, showed quite similar results as our registry: the cumulative incidence of major adverse cardiac events was 5.7% at six months and target lesion

revascularization was 3.4% at 180 days.[33] Given the fact that no angiographic follow-up was performed, this might explain the low rate of TLR, besides the chosen and described less traumatic technique of the procedure.

Limitations

The main drawback of our technique is that it can not be applied in angles less than 40º -50º, due to potential excessive protrusion of the stent struts of the SB stent into the lumen of the MB. Even in wider angles, though, the possibility of protrusion of the side branch stent struts toward the side branch lumen cannot be fully excluded even when using the " cushion technique " against the MB balloon. A final kissing balloon dilatation may have a favorable role in these cases, mainly regarding the issue of stent thrombosis. Although we describe a low rate of (sub-) acute stent thrombosis a final kissing balloon technique might have reduced this number even further. Our reasons for not performing this have been extensively described above.

The major clinical limitation of this registry is the lack of angiographic follow-up in the majority of our patients. Follow up also did not include systematic stress testing. This could eventually have underestimated the incidence of silent ischemia , especially in the diabetic population.

CONCLUSION

This study implies that in a preselected population of patients with severe bifurcation lesions, this new approach of modified T stenting with "minimal crush' was technically feasible and showed a low incidence of procedural complications and clinical events after a six months follow-up period. A practical advantage is that the technique is quite safe and relatively simple to execute. It is therefore a promising strategy that should be added to the current techniques that are being used and evaluated for this purpose, with either bare-metal or drug-eluting-stents. Further evaluation of this technique is required in trials with angiographic follow-up, comparing it with other techniques that are currently being used for the treatment of bifurcation lesions.

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11

Safety and Efficacy of Drug-Eluting Balloons in Percutaneous Treatment of Bifurcation Lesions: The DEBIUT (Drug-Eluting Balloon in BIfurcaton UTrecht)Registry.

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ABSTRACT

Objectives

To evaluate outcomes after percutaneous coronary intervention (PCI) with a drug-eluting balloon catheter (paclitaxel-coated) in patients with coronary artery bifurcation lesions.

Background

The current practice of provisional stenting of the main branch (MB) is reasonable; however, long-term results of side-branch (SB) treatment are suboptimal. The use of drug-eluting stents has not improved these results, regardless of the implantation technique, and could potentially lead to a significant increase in (late) thrombotic events. To evaluate short-term safety and efficacy of a drug-eluting balloon (DEB) in patients with bifurcation lesions followed by provisional stenting of the main branch, we set up the DEBIUT Registry.

Methods

This registry enrolled 20 eligible patients with coronary artery bifurcation lesions. Patients received a PCI with a paclitaxel-coated balloon catheter, followed by provisional stenting of the MB with a bare-metal stent. Acute angiographic and clinical follow-up were performed after 1 and 4 months.

Results

The procedure was successful in all patients. The use of sequential predilatation with DEB was safe and well tolerated. No acute or subacute closure of side branches occurred after treating with DEB. All patients were treated according to the provisional stenting technique; no stents were placed in the SB. At 4-month follow-up no major acute coronary events and no subacute vessel closure were reported.

Conclusion

The use of a drug-eluting balloon in patients with bifurcation lesions was effective and safe up to four months following PCI in patients with coronary artery bifurcation lesions.

INTRODUCTION

The treatment of bifurcated coronary artery stenosis remains one of the most difficult and challenging lesions. Percutaneous coronary intervention (PCI) in bifurcation lesions (BiF) is associated with lower immediate angiographic and clinical success and higher rates of restenosis, which furthermore, are more challenging to treat compared to non-bifurcated lesions. The introduction of the drug-eluting stents (DES) seems to have had less of an impact on PCI results [17,18,19] in bifurcation lesions. Furthermore, it has been reported recently that especially in complex lesions, rates of subacute thrombosis and even mortality are high in patients treated with drug-eluting stents [20,21].

The implementation of a variety of bifurcation-specific PCI techniques [1-11] has improved the acute angiographic and procedural success to acceptable rates (over 95% and ~90% respectively) [12-15]. Current knowledge and experience provide almost universal agreement that whenever possible, stenting only of the main branch with the jailed-wire technique and final kissing balloon should be the strategy of choice [15]. Thus the current practice of stenting only (whenever possible) the main branch with DES is reasonable, but the results of side-branch treatment are suboptimal and there is room for improvement especially regarding long term side branch treatment.

Recently, non-stent-based local balloon delivery systems of antiproliferative drugs have been developed. These drug eluting balloons might improve the current results of side-branch treatment and overcome some of the late disadvantages of the drug-eluting stents. Such an approach would obviously not halt recoil, but it should efficiently diminish the component of restenosis due to proliferation / hyperplasia [22], especially in bifurcation lesions. If its side-branch-restenosis prevention capability is proved, the temptation to deploy a second stent in the side branch may be best resisted, simplifying the procedure and in turn may improve overall outcomes of PCI in bifurcation lesions with regard to restenosis and late-stent thrombosis.

The aim of this registry was to study the safety and efficacy of the use of drug-eluting balloons in bifurcation lesions with sequential predilatation of side branch and main branch, followed by provisional stenting of the main branch.

MATERIALS AND METHODS

Registry setup

Patients with bifurcation lesions were enrolled and received PCI with the DIOR drug-eluting balloon catheter. The registry was notified and approved by the institutional ethics committee, and all patients provided written informed consent.

Inclusion/exclusion criteria

Patients with lesions involving a de novo coronary artery bifurcation lesion located at a side-branch point with a main vessel diameter of ≥2.5 mm and with a SB diameter of ≥2 mm were eligible for the study. See Table I for inclusion and exclusion criteria.

Dior™ balloon

The Dior™ balloon has a paclitaxel-coated balloon surface, containing 3 μg paclitaxel / mm^2. The drug is contained within the nano-porous balloon surface, with paclitaxel microcrystals (following dimethylsulfate treatment). For protection of potential wash off effect of the drug during manipulation in the guide and vessel, the drug is hidden within the balloon folds. The preclinical findings revealed no concerns as per the pharmacological and toxicological properties. In acute experimental settings the tissue concentration after deployment was found to be 0.3 to 0.5 μM [16], which is well within the effective range for single-dose applications of paclitaxel without leading to unspecific apoptosis [17]. The recommended balloon inflation time is 45 to 60 seconds at nominal balloon pressure, during which 30 to 45% of the paclitaxel is released to the vessel wall.

Table I. Inclusion/exclusion criteria

Inclusion criteria
• Stable angina pectoris (CCS class 1, 2 ,3, 4) or unstable angina and documented ischemia or silent ischemia
• Patients eligible for coronary revascularization
• The target bifurcation lesion has a major native coronary artery (≥2.5 mm) with a stenosis ≥50% (on visual assessment) located at a side branch (≥2 mm)
• Patient must be acceptable for CABG
• De novo lesion
• The main vessel lesion can be covered by one stent (up to 32 mm)
• Only one target lesion can be included in the study: other lesions in different vessels are successfully treated before the treatment of the target lesion (residual stenosis <30%; stent well deployed; no residual dissection; normal TIMI flow; no chest pain; ECG unchanged compared to pre-procedural ECG)
• Signed informed consent
Exclusion criteria
• Patient unable to give informed consent
• Left ventricular ejection fraction ≤30%
• Patients with a previous PCI in the target vessel
• Patients with left main disease
• Severe calcifications with an undilatable lesion during balloon predilatation
• History of bleeding diathesis
• Untreated significant lesion >50% diameter stenosis remaining proximal or distal to the target intervention.
• Acute myocardial infarction
• Allergy to contrast and/or required anti-platelet medication

Abbreviations: CABG=coronary artery bypass grafting; CCS=Canadian Cardiovascular Society; ECG=electrocardiogram; PCI=percutaneous coronary intervention; TIMI=Thrombolysis In Myocardial Infarction

Interventional procedure

All patients enrolled in the registry were treated with acetylsalicylic acid 325 mg and a 300 mg loading-dose of clopidogrel 12 and 2 hours before the procedure, respectively. Heparin was administered intravenously to maintain an activated clotting time ≥250 seconds during the procedure. Administration of glycoprotein IIb/IIIa inhibitors was left to the physician's discretion.

The technique for the lesion treatment was a stepwise strategy according to the "provisional T-stenting" approach. Two 0.014-guide wires were placed in the main target vessel and

the SB. Balloon predilatation with regular balloons of both vessels was performed first at low pressure (6 to 8 atmospheres) as usual, followed by sequential drug eluting balloon inflations (8 atmospheres for 60 seconds) in the main and side branch, respectively. Special care was taken to record each balloon inflation to avoid too much of a balloon overlap in the main branch and potential geographical miss after stent placement in the main branch (see flow chart Figure I).

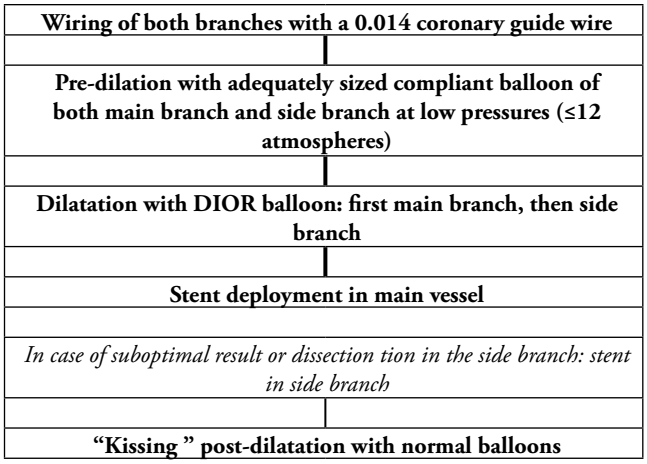

Figure I. Flow chart

Once satisfied with the angiographic result, the main branch was stented with a bare-metal stent (BMS) leaving the side branch wire in place ("jailed wire" technique). After recrossing with the wires, a final kissing-balloon inflation with regular balloons was performed according to routine practice. The procedure was completed when the result met the criteria of angiographic success (TIMI 3 flow in the main and side branch with a diameter stenosis <10% and <40%, respectively). For an example of a successful procedure, see Figure II to VIII.

Acetylsalicylic acid was continued indefinitely after the procedure and clopidogrel (75 mg/day) for 3 months only.

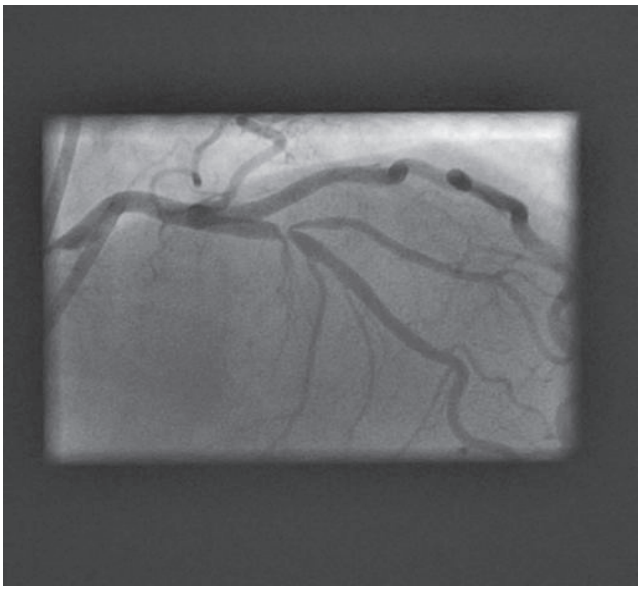

Figure II. Bifurcation LAD/D1

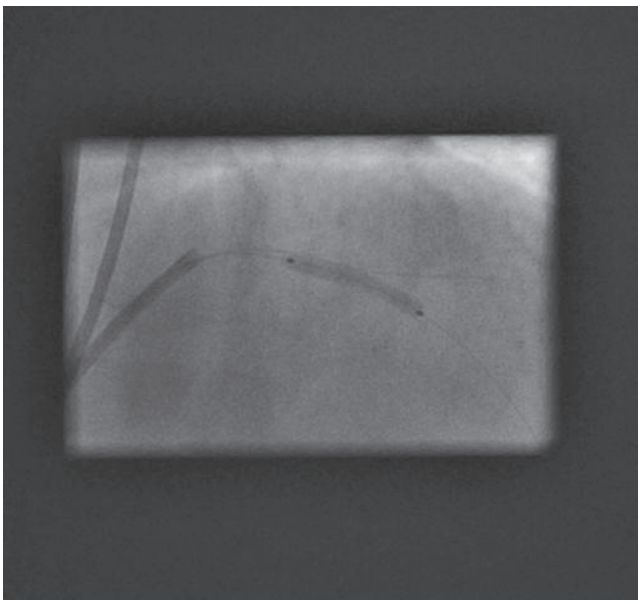

Figure III. After wiring and predilatation with regular balloons, dilatation with 3.0x25 mm Dior™

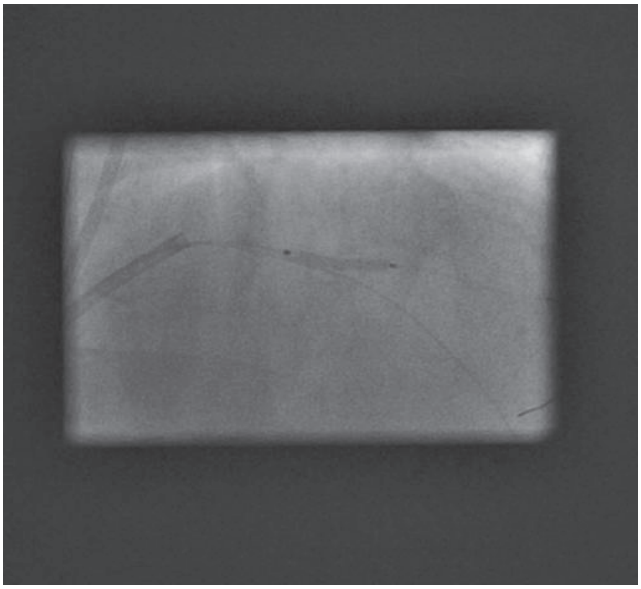

Figure IV. Followed by dilatation of the sidebranch with 2.0 x 20 mm Dior™

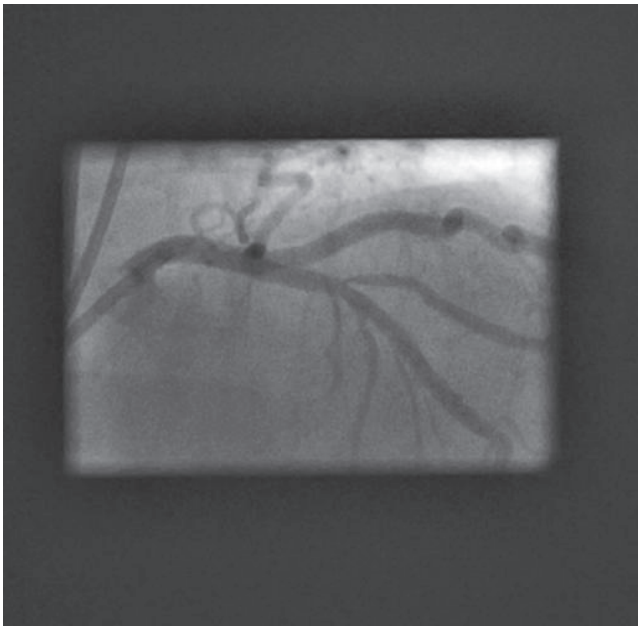

Figure V. Result after Dior™ dilatations

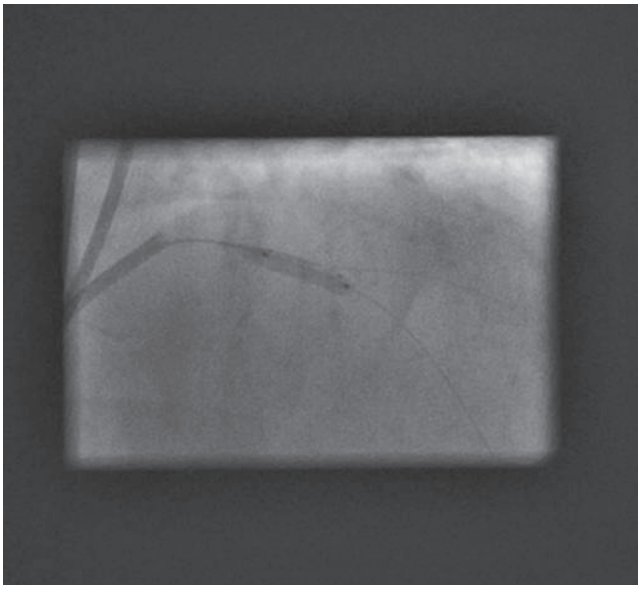

Figure VI. Placement of 3.0 x 15 mm Crono™ stent (bare metal)

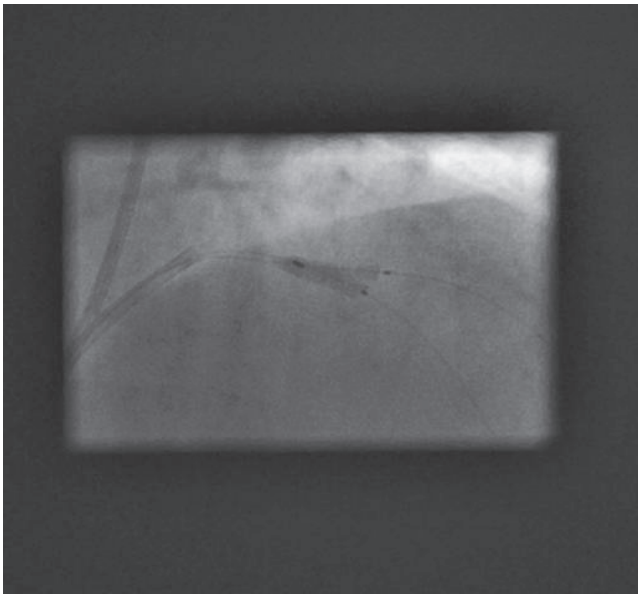

Figure VII. "Kissing" postdilatation with regular balloons

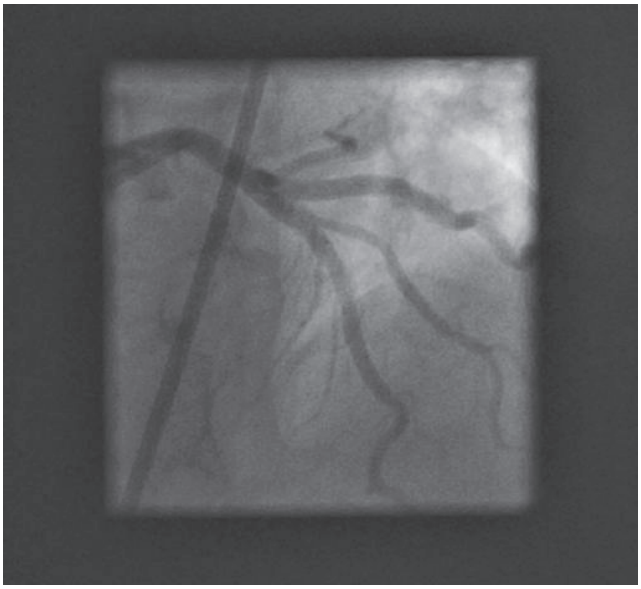

Figure VIII. Final result

Follow-up and endpoints

All patients were contacted by phone and interviewed on clinical status one month and four months after the procedure. Major acute coronary events (MACE) were defined as all cardiac deaths, Q-wave and non-Q wave myocardial infarction, target-lesion failure (defined as both the MB and SB) including PCI and CABG.

Statistical analysis

Descriptive statistical methods were used to describe the data. Continuous variables were presented as mean ±SD, categorical variables were presented as counts and percentages. No confirmatory analyses were performed.

RESULTS

Patient characteristics

Twenty patients with suitable bifurcation lesions were treated according to protocol between June and August 2007. Baseline patient characteristics are shown in Table II.

Table II. Baseline characteristics

Characteristics	**Number of patients (n = 20)**
Age (years [range])	68 (41 – 78)
Male sex, *n* (%)	14 (70)
Current or ex-smoker, *n* (%)	15 (75)
Hypercholesterolemia, *n* (%)	16 (80)
Hypertension, *n* (%)	14 (70)
Diabetes mellitus, *n* (%)	6 (30)
Previous myocardial infarction, *n* (%)	5 (25)
Previous CABG, *n* (%)	5 (25)
LVEF, %	49
Glycoprotein IIb/IIIa inhibitor use, *n* (%)	4 (20)
Lesion characteristics	
LAD/diagonal, *n* (%)	17 (85)
LCX/OM, *n* (%)	1 (5)
LM/LAD/LCX, *n* (%)	0 (0)
RCA/RCA-PL/RCA-PD, *n* (%)	2 (10)

Abbreviations: CABG=coronary artery bypass grafting; LAD=left anterior descending artery; LCX=left circumflex artery; LVEF=left ventricular ejection fraction; OM=obtuse marginal; PD=posterior descending; PL=posterior lateral; RCA=right coronary artery; SD=standard deviation

Most lesions were located at the left anterior descending artery/diagonal branch bifurcation. For baseline bifurcation anatomy (Medina classification [18]) see Table III.

Table III. Baseline bifurcation anatomy – Medina classification [32]

Medina classification type: (proximal main branch, distal main branch, and side branch involvement	**Number of patients (n = 20) (n [%])**
1.1.1	12 (60)
1.1.0	2 (10)
1.0.1	4 (20)
0.1.1	2 (10)

Quantitative coronary angiography (QCA) analysis results after the procedure are shown in Table IV. Due to the nature of this registry no follow-up QCA is reported.

Table IV. Quantitative coronary angiography analysis

	Main branch	Side branch
Lesion length (mm)	15.5 +/- 5.0	4.2 +/- 2.8
Stent length (mm)	19.0 +/- 6.0	-
Reference vessel diameter (mm)	3.0 +/- 0.6	2.4 +/- 0.4

The procedure was successful in all twenty patients. All side branches were treated with a 2.0 x 20 mm DIOR balloon. Glycoprotein IIb/IIIa inhibitors were used in 4 procedures due to some haziness at the side branch ostium. However, no flow-limiting dissections or acute closure of sidebranches was observed for which additional stenting in the side branch was required. The balloons and stents used in the main branch are shown in Table V and Table VI. Because safety and long-term data on the use of drug-eluting-balloon combined with drug-eluting stents are lacking, this combination was not used in this study.

Table V. Drug-eluting balloons used in the study[a]

Location	Numbers	Size
Side branch	20	2.0 x 20 mm
Main branch	16	3.0 x 25 mm
	3	2.75 x 25 mm
	1	3.5 x 25 mm

[a] Inflation at 8 atmosphere for 1 minute according to instructions for use

Table VI. Stents placed in main branches

Size in mm	Numbers
2.75 x 18	3
3.0 x 15	14
3.0 x 25	2

Angioplasty

The primary procedure was successful in all 20 patients. For baseline angiographic findings see Table II.

Follow-up

Patients were contacted after 1 month and 4 months; all were symptom free at follow-up. No MACE or reintervention had occurred.

Adverse events

No serious adverse events were reported during the 4-month follow-up period. Adverse events were reported in 5 patients (see Table VII for details). Phlebitis and small groin hematoma in 3 patients were considered related to the performed procedure, whereas a skin rash and paroxysmal atrial fibrillation were unrelated. Remarkably no late thrombosis was reported so far, although all patients stopped Clopidogrel 3 months after the index procedure.

Table VII. Adverse events

Patient number	Time and type of event	Relationship to procedure	Outcome
2	Day 1: phlebitis in left hand due to intravenous line	Related	Complete recovery
6	Day 8: skin rash possibly due to clopidogrel	Not related	Complete recovery
9	Day 1: paroxysmal atrial fibrillation	Not related	Complete recovery
12	Day 1: small groin hematoma	Related	Complete recovery
17	Day 1: small groin hematoma	Related	Complete recovery

DISCUSSION

Despite the development in the treatment of bifurcation lesions, these lesions are still known to have a suboptimal clinical outcome, compared to straight single-lesion PCI, due to a lower acute success rate and a high risk of restenosis, especially in the SB.

In previous years, side branch lesions were mainly treated with balloon dilatation. However, later the use of bare-metal stents was considered necessary to reduce the rate of acute vessel closure, but this was accompanied with a higher rate of restenosis.

The introduction of DES showed in general a reduction in late in-stent restenosis compared with bare-metal stents. However, the initial promising results of DES were not reproducible in the special circumstances of bifurcation lesions as the rates of restenosis in the side branch remained high. Data from the Nordic Bifurcation Study show that the method of choice is stenting the main branch and only dilating the side branch, because double stenting appears not to lower the risk of restenosis [15].

At first the anatomical configuration of bifurcation lesions, with the consequence of an abnormal flow pattern within the bifurcation, is probably an important cause of restenosis. The second important factor is the inhomogeneous area of the stent struts which are not covering the full circumferential bifurcation ostium.

It should be noted that according to recent reports the rates of subacute thrombosis and even mortality might be higher in patients especially with complex lesions treated with DES [19].

Drug-eluting-stents were developed with the knowledge that the process of restenosis development is a slow process. Therefore, drug release from the stent is deliberately prolonged with the use of special polymer coatings, providing a long-term and sustained drug release.

Surprisingly, laboratory results showed that even a short contact between taxane compounds and vascular smooth muscle cells can inhibit the proliferation of the cells for a long period, so a stent-driven sustained drug release does not seem to be necessary at all [20].

This was confirmed in animal experiments, where paclitaxel was delivered into coronary arteries using a contrast medium or a paclitaxel-coated balloon catheter. Both methods significantly reduced neointimal proliferation with a more pronounced reduction in the paclitaxel-coated balloon group [21].

In addition, about 85% of the stented coronary artery area is not covered by the stent struts, resulting in inhomogeneous drug distribution. This may yield a less effective result

than initially thought. Balloon-catheter drug delivery on the other hand, makes a direct effective homogeneous intracoronary drug delivery possible without the disadvantages of the DES. The Paccocath ISR trial [22] was the first to demonstrate a significant reduction in the incidence of restenosis by using the paclitaxel-coated balloon compared with PCI with an uncoated balloon. The lesions-to-treat were restenotic lesions in a stented coronary artery.

The potential advantages of the use of DEB in bifurcation lesions are (1) homogeneous administration of the drug, whereas the DES only delivers paclitaxel in the proximity of the struts; (2) delivery of high drug concentrations at the vessel wall at the moment of injury; (3) avoidance of potential late stent thrombosis; and (4) respecting the original anatomy of the bifurcation carina, leaving no stent scaffold and hence diminish abnormal flow patterns within the bifurcation.

This registry investigated the short-term safety and efficacy of a drug-eluting balloon for PCI in coronary bifurcation lesions after sequential dilatation and final placement of a stent in the main branch. The procedure is easy and safe to perform and yielded excellent short-term results with an acute success rate of 100%. To our knowledge this is the first report on the use of the drug-eluting-balloon in patients with bifurcation lesions.

The major limitation of this registry is the short clinical follow-up period. However, the main purpose of this study was to show the safety and efficacy of the drug-eluting-balloon under the special circumstances of the bifurcation lesions.

CONCLUSIONS

The use of paclitaxel-coated balloon catheters is effective and safe in PCI for coronary artery bifurcation lesions, without clinical signs of restenosis at 4 months follow up. Although all patients stopped Clopidogrel at 3 month after the index procedure so far no late thrombosis was reported.

This registry provides encouraging results with respect to the safety and efficacy of the drug-eluting balloon. Stenting of the side branch does not lower the rate of restenosis,

while the placement of two stents in BiF makes the procedure more difficult to perform. The drug-eluting-balloon makes the procedure easier and may even lower long-term restenosis rates in the side branch.

Future randomized studies need to compare the use of the drug-eluting-balloons and drug-eluting-stents in Bifurcation lesions and assess the long-term efficacy and safety of the drug-eluting balloon.

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12

One-year clinical follow-up of a registry evaluating a new generation thin-strut bare cobalt-chromium stent in selected patients with obstructive coronary artery disease

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ABSTRACT

Aim

To evaluate clinical events in a specifically selected cohort of patients with obstructive coronary artery disease (CAD), using a new generation thin-strut bare cobalt-chromium coronary stent.

Methods

Patients with single or multi-vessel, stable or unstable CAD undergoing percutaneous coronary intervention (PCI) and eligible for implantation of at least 1 bare cobalt-chromium stent were retrospectively evaluated in a single-center registry. Pre-specified criteria for bare cobalt-chromium stent implantation in our center were: any acute ST elevation myocardial infarction (MI), otherwise 1) de novo coronary lesion, and 2) lesion length <20 mm, and 3) reference vessel diameter >2.6 mm, and 4) no diabetes, unless reference vessel diameter >3.5mm. Endpoints were death, MI and clinically driven target lesion revascularization (TLR) and target vessel revascularization (TVR) after 12 months.

Results

Between September 2005 and June 2007, 712 patients (48.7% 1-vessel, 29.9% 2-vessel, 20% 3-vessel and 1.4% left main disease; 7.9% diabetics) were treated with 800 bare cobalt-chromium stents, for stable angina (40.9%), unstable angina (20.9%) or acute ST elevation MI (38.2%). The procedural success rate was 99.3%. Peri-procedural MI rate was 2.2% in the semi-elective group. At 12 months there were 17 deaths (2.4%), of which 9 non cardiac, 20 (2.8%) MI, 19 (2.7%) TLR and 29 (4.1%) TVR. Early and late definite stent thrombosis occurred respectively in 4 (0.6%) and 3 (0.4%) patients.

Conclusions

A strategy combining a pre-specified simple selection process and the use of a new thin-strut bare cobalt-chromium stent is safe and effective at 1-year clinical follow-up.

INTRODUCTION

Percutaneous coronary interventions (PCI) are a valuable addition to treatment regimens in modern cardiology (1-3). The use of intracoronary metallic stents has improved results over balloon dilatation alone and has become standard care for patients undergoing PCI (4). However, in-stent restenosis, leading to recurrence of symptoms, has been the major drawback of bare metal stents (BMS) (5). Drug eluting stents (DES) have been introduced in an attempt to overcome this problem and, due to the improved effectiveness in preventing restenosis, DES implantation has rapidly grown in up to 80% of cases in some countries (6). However, recently there have been concerns about their long term safety (7), due to an increase in late stent thrombosis, possibly linked to a delayed endothelialization of the stent struts. Delayed endothelial cell growth is due to a non selective inhibitory action of the drug on targeting both smooth muscle cell proliferation and endothelial cell regeneration (8). Moreover, DES definitely increases the cost of PCI when compared to BMS and debate is ongoing over the long-term cost-effectiveness of these devices (9).

The beneficial clinical data of DES are mainly derived from trials comparing DES with first generation thick-strut stainless steel BMS. However, outcomes can be different between stents depending on material and design (10-13). Stents with thinner struts have shown less restenosis and less repeated interventions (14-15). This effect may be due to more rapid re-endothelialization after deployment of thinner-strut stents, reducing vascular injury and inflammation (14-16). With the progressive development of the BMS manufacturing, the use of cobalt-chromium alloy has appeared promising. This alloy has shown good biocompatibility and appeared to limit the adverse proliferative response seen with other alloys (9-11). In addition, cobalt-chromium compared with stainless steel, allows reduction in strut thickness with increased flexibility, conserving both radial strength and deliverability (17).

Our aim was to evaluate the clinical outcome of a cohort of patients undergoing PCI, in whom the decision to use a new generation thin-strut bare cobalt-chromium coronary stent was pre-specified according to "non-DES" criteria.

METHODS

This was a single-center retrospective registry in which the Skylor thin-strut bare cobalt-chromium stent (Invatec Corporation, Italy) was used. As the stent was already marketed at the beginning of the study, no formal informed consent, apart from the one related to the procedure, was requested.

Procedures

All angioplasty procedures were performed according to routine practice. Type of stent used was at the discretion of the operator within the center consensus agreements (18), which limit the use of BMS to patients with the following criteria: any acute ST elevation myocardial infarction (MI), otherwise 1) de novo coronary lesion, and 2) lesion length <20 mm, and 3) reference vessel diameter >2.6 mm, and 4) no diabetes, unless reference vessel diameter >3.5mm. Exceptions, with use of BMS also out of these criteria, occurred in case of predicted or suspected impossibility for patients to assume long-term (1 year) double antiplatelet therapy or in case of expected survival < 6 months. According to the daily routine, direct stenting and post-dilatation were allowed and left to the discretion of the operator. Patients who received different types of stents in the index vessel were excluded. All patients were treated with standard optimal medical therapy, consisting of aspirin (at least 80 mg/day lifetime) and clopidogrel (75 mg/day after loading dose of 300 or 600 mg for at least 3-6 months or 1 year in case of acute coronary syndromes). Use of beta-blocker, ACE-inhibitor, calcium-antagonist, statins and nitrates were administered if clinically indicated.

Stent characteristics

The Skylor stent is a thin-strut bare cobalt-chromium stent with a multiple mono-type closed cell design. Strut thickness differs according to the diameter of the stent implanted: 70 µm for small vessel stents (2.00, 2.25 or 2.50 mm in diameter), 80 µm for medium vessel stents (2.75, 3.00 and 3.50 mm in diameter) and 95 µm for large vessel stents (4.00, 4.50 and 5.00 mm in diameter) (19).

Data collection

All PCI performed were recorded in a local data management system. Data input included medical history, risk factors, medication use, peri-procedural data and clinical follow-up. For this analysis all patients who underwent PCI involving at least one Skylor-stent between September 2005 and June 2007 were included. Active follow-up by phone call following a pre-specified questionnaire are routinely performed in our institute for all patients treated with

PCI at 1 and 12 months after the index procedure.

Endpoint definitions

In case an event occurred, careful review of the in-hospital data or requirement of data from other hospitals were performed in order to classify the event. All deaths were considered cardiac unless a clear non-cardiac cause could be established. Specifically, any unexpected or unwitnessed death was considered of cardiac origin. Myocardial infarction was defined as anginal symptoms associated with Creatine Kinase levels >3 times the upper limit of normal and concurrent elevation of Creatine Kinase-MB above the upper limit of normal (according to local reference values). All reported repeated interventions in the stented segment (including the stent and the 5 mm proximal and distal to the stent) were classified as target lesion revascularization (TLR). Repeated interventions in the same vessel were reported as target vessel revascularization (TVR). Major adverse cardiac events (MACE) were defined as a combined endpoint of death, MI (including periprocedural MI) and TVR. Stent thrombosis was defined according to the Academic Research Consortium criteria (20).

Statistical analysis

Analyses were performed using the Social Science package SPSS for Windows version 14.0 (SPSS Inc., Chicago, Illinois). Continuous data are reported as means and standard deviations. Dichotomous data are reported as numbers (percentages). Due to the observational, non-randomised nature of this study, only descriptive statistics are reported. For every endpoint evaluated, 95% confidence intervals (CI) of the incidence

rate were calculated, using dedicated software (Confidence Interval Analysis, Version 2.0.0, available at: http://www.medschool.soton.ac.uk/cia/main.htm, last visit: 26 February 2009).

RESULTS

Baseline characteristics and in-hospital clinical outcomes

A total of 712 consecutive patients treated with PCI involving deployment of at least one Skylor stent were included. Baseline patient characteristics are shown in table 1. In total 800 Skylor stents were implanted. Procedural data are shown in table 2. One Skylor stent was implanted in 603 (84.6%) of the cases and 2 stents in 85 (11.9%). In 5 PCI, 4 Skylor stents were used, and in 1 PCI, 7 Skylor stents were implanted (these 5 procedures concerned technically challenging chronic total occlusions). The procedural success rate was 99.3% (95% CI: 98.1-99.9%): in 3 PCI the stent could not be delivered at lesion site; additionally one PCI in a saphenous venous graft was complicated by perforation of the vessel treated, which was successfully managed with deployment of a covered stent; a second PCI was complicated by catheter-induced (type E) left main dissection, successfully treated with uneventful urgent coronary artery bypass surgery, which was also the sole TLR in-hospital. There were 4 in-hospital deaths (0.6% [0.1-1.4%]). Three patients died in the catheterization laboratory, all presenting with an acute MI complicated by cardiogenic shock and referred while intubated and under inotropic support. Another patient underwent successful primary PCI for acute anteroseptal MI and, because of hemodynamic instability, he was transferred to the coronary care unit, were he died 2 days later because of ventricular tachyarrhythmia (probably due to early stent thrombosis). There were 10 peri-procedural MI (2.2% [1.2-4.1%]) in the semi-elective group (440 patients, 291 stable and 149 unstable).

Table 1. Baseline patient characteristics.

	Patients (N=712)
Age (Years)	64 ± 13
Male gender	530 (74.4%)
Risk factors	
Diabetes	56 (7.9%)
Hypertension	238 (33.4%)
Hypercholesterolemia	257 (36.1%)
Current smoking	156 (21.9%)
Family history	247 (34.7%)
Previous myocardial infarction	154 (21.6%)
Previous percutaneous coronary procedure	106 (14.9%)
Previous coronary bypass surgery	51 (7.2%)
Previous cerebrovascular accident	36 (5.1%)
Baseline angina status	
Stable	291 (40.9%)
Acute coronary syndrome	149 (20.9%)
Acute ST elevation myocardial infarction	272 (38.2%)
Extend of disease	
One vessel	347 (48.7%)
Two vessels	213 (29.9%)
Three vessels	142 (20.0%)
Left main	10 (1.4%)
Left ventricular function	
Poor	21 (3.0%)
Moderate	213 (29.9%)
Normal	478 (67.1%)

Table 2. Procedural data.

	Procedures (N=712) **Lesions (N=785)**
Procedures with 1 Skylor stent	603 (84.6%)
Procedures with 2 Skylor stents	85 (11.9%)
Procedures with >2 Skylor stents	8 (1.2%)
Average stent length (mm)	15.5 ± 6.2
Average stent diameter (mm)	3.1 ± 0.3
Procedural success	709 (99.6 %)
Type of percutaneous coronary intervention	
Single vessel	639 (89.7%)
Multi-vessel	73 (10.3%)
Index vessel	
Left anterior descending artery	334 (42.5%)
Right coronary artery	278 (35.4%)
Circumflex artery	148 (18.9%)
Left main coronary artery	10 (1.3%)
Bypass graft	15 (1.9%)
Lesion type (ACC/AHA classification)	
A	120 (15.3%)
B1	336 (42.8%)
B2	201 (25.6%)
C	128 (16.3%)

Thirty-day clinical outcomes

One-month clinical events are shown in table 3. There were 5 repeated PCI procedures between hospital discharge and 1 month, one of which occurred because of TLR caused by dissection which was missed at the index procedure. The remaining 4 procedures (0.6%) were due to early stent thrombosis, all causing an acute MI.

Table 3. Follow up data.

	Patients (N=712)
In-hospital adverse events	
Death	4 (0.6%)
Periprocedural myocardial infarction (in the semi-elective group)	10 / 440 (2.2%)
Cerebrovascular accident	1 (0.1%)
Target lesion revascularization	1 (0.1%)
Access site complications	8 (1.1%)
Cumulative 30-day adverse events	
Death	4 (0.6%)
Myocardial infarction	14 (2.0%)
Cerebrovascular accident	1 (0.1%)
Target lesion revascularization	6 (0.8%)
Target vessel revascularization	6 (0.8%)
Definite early stent thrombosis	4 (0.6%)
Cumulative 12-month adverse events	
Death	17 (2.4%)
Myocardial infarction	20 (2.8%)
Cerebrovascular accident	1 (0.1%)
Target lesion revascularization	19 (2.6%)
Target vessel revascularization	29 (4.1%)
Major adverse cardiac events	59 (8.3%)
Definite early and late stent thrombosis	7 (1.0%)

Twelve-month clinical outcomes

One-year clinical events are presented in table 3. There were 3 patients lost to follow-up at 12 months (0.4%). The overall mortality rate was 2.4% (1.3-4.2%) with 4 additional cardiac deaths (all possible stent thromboses) between 1 and 12 months follow-up and 9 (1.3%) non cardiac deaths (all due to tumors). The total rate of MI was 2.8% (2.1-4.5%), with 6 additional MI (all considered late stent thromboses, 3 definite and 3 probable) between 1 and 12 months. The rate of TLR was 2.7% (1.8-4.4%) including

3 PCI performed for definite late stent thrombosis and 10 revascularization procedures performed for recurrent ischemia. The rate of TVR was 4.1% (2.8-6.1%). Overall, out of the 29 TVR procedures, 28 were again percutaneous, while 1 was surgical. The overall rate of definite and probable stent thrombosis was 1.5% (0.9-3.1%), including 5 early cases and 6 late cases. Overall MACE rate was 8.3% (6.7%-11%).

DISCUSSION

Drug-eluting stents are more effective than BMS in reducing restenosis and preventing repeated revascularization procedures (6), mainly by limiting intimal hyperplasia (21), with similar early rates of death or nonfatal MI. However, concern is growing that delayed endothelialization, incomplete neointimal healing, or hypersensitivity reactions after the implantation of DES may lead to increased rates of late adverse events, such as cardiac death and MI, due to the occurrence of stent thrombosis (7,8).

In order to minimize late thrombotic events with the use of DES, an extended dual antiplatelet regiment is recommended for at least 12 months. However, the bleeding risks associated with prolonged dual antiplatelet therapy (22,23) and the increased costs for the healthcare system (9) should be taken into account. Moreover, a substantial proportion of patients has contraindications to prolonged antiplatelet therapy, or takes already oral anticoagulants or cannot afford the increased cost of clopidogrel, in countries where this drug is not reimbursed. Therefore, such a prolonged dual antiplatelet therapy may be valuable only in patients who are at increased risk for stent thrombosis after DES implantation, such as those with diabetes, renal failure, long lesions and bifurcation disease (24,25). These patients have an increased risk for in stent restenosis (ISR). Patients with an increased risk for ISR in general benefit more from DES in terms of reduction of restenosis. However, independently from clopidogrel use, in randomized trials as well as in large registries, very late stent thrombosis (occurring >1 year after stent implantation) is more common after DES than BMS implantation (7,26). Thus, in "real-world" patients the selective use of BMS can be adequately justified, when safety is the first issue. However, the overall efficacy of BMS is sub-optimal as compared to DES.

The detection of selected subgroups of patients and lesions where BMS can perform well with a low rate of repeated revascularizations appears a reasonable alternative. Some data from registries and post-hoc analyses of randomized controlled trials suggest that BMS favorably compare to DES in lesions located in large coronary vessels (defined as vessels in which a stent >3.0 mm in diameter was implanted) (27-29). Angiographic superiority of DES remains solid, even in comparison with the newer generation BMS. In a recent randomized trial, angiographic parameters of restenosis were significantly lower in the DES group versus a thin-strut cobalt-chromium stent (late loss: 0.18 ± 0.40 versus 0.58 ± 0.51 mm). Though, the angiographic performance of BMS in this trial was good. Furthermore, no statistically significant clinical differences between the two groups were apparent at 12 months (the trial however was definitely underpowered for this endpoint): freedom from target vessel failure at 12 months was 72% for DES patients and 68% for BMS patients (30). Other categories where conflicting results with DES still exist are patients with acute ST elevation MI and lesions in saphenous vein grafts (SVG). Regarding acute ST elevation MI, recent registries have shown no clear superiority of DES over BMS in terms of long-term repeated revascularizations (31), raising even doubts on a possible increase in long-term mortality after DES placement (32). However, in a recent meta-analysis of randomized trials, the use of DES significantly reduced the short-term rate of TVR without impact on mortality (33). Regarding SVG stenting, the data comparing DES with BMS are scarce and even more conflicting. In a secondary post-hoc analysis of a randomized trial the use of DES was found to be associated with increased long-term mortality as compared with BMS (34). Nevertheless, these data need further verification.

In light of all these issues, it is obvious that in the modern era of interventional cardiology there is a place for the newest generation of BMS. In the aforementioned subgroups of patients in whom the use of DES seems not completely beneficial or is based on contradictory trials, as well as in patients with relative or absolute contraindication to prolonged antiplatelet therapy, the new generation of thin-strut cobalt-chromium BMS fills the gap with very good efficacy. Actually according to our contemporary policy, providing that the patients do not have an acute ST elevation MI and can assume double

oral antiplatelet therapy for 1 year, DES should be reserved for the following indications: 1) In-stent restenosis, 2) diabetes mellitus with reference vessel diameter <3.5 mm, 3) small vessel disease (reference vessel diameter <2.6 mm), and 4) lesions with length >20 mm. Our registry confirms that this policy provides very good results with a new generation BMS in non-high-risk patients that do not fulfill the above mentioned criteria. This new generation class of cobalt chromium thin-strut bare metal stents has been adequately tested in several registries and in a variety of clinical settings. In each of these studies, newer generation BMS seem a safe and effective treatment modality (table 4) (17,35-38). Besides these promising results, there are also some technical advantages related to these BMS. Since cobalt chromium is about 75% stronger than stainless steel, it allows the stent to have thinner struts, thus increasing pushability, flexibility, deliverability and trackability (potentially making the PCI procedure simpler and faster), while maintaining radial strength and radiological visibility.

A final proof of the substantial similarity in effectiveness and superiority in safety of these new generation BMS as compared to DES will come from the ongoing BASKET PROVE randomized trial, performed specifically in lesions in large coronary vessels and planning to enroll more than 2000 patients (39).

Table 4. Literature on bare cobalt-chromium coronary stents.

Stent type	**Follow-up duration (months)**	**N. of patients**	**Procedural success (%)**	**TLR (%)**	**TVR (%)**	**MACE (%)**	**TVF (%)**	**Stent Thrombosis (%)**
MultiLink Vision (17)	6	268	99.0	4.3	5.1	6.2	6.7	-
Medtronic Driver (35)	9	298	98.3	7.0	8.1	8.4	8.1	0
Medtronic Driver (36)	6	202	98.0	9.4	-	12.4	-	0.5
Arthos Pico (37)	12	203	98.0	-	8.9	15.0	-	2.0
Invatec Skylor (38)	9	150	97.0	6.0	-	8.0	12.4	1.4

MACE: major adverse cardiac event; TLR: target lesion revascularization; TVF: target vessel failure; TVR: target vessel revascularization. Each endpoint was defined according to the specific study.

Limitations

We acknowledge that this is a single centre registry. Lack of randomization and retrospective design can be regarded as limitations. Furthermore, patients did not undergo systematic angiographic follow-up, but they received a control angiogram only if clinically indicated. Thus there is no angiographic evaluation of the performance of the stent. On the other hand, this registry reflects every day clinical practice. We report the clinical performance of the stent, instead of using surrogate angiographic measurements to attain derived endpoints. It is also well known that routine angiographic follow-up tends to inflate the rate of repeated revascularization procedures due to the so called "oculo-stenotic" reflex (40).

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Summary and conclusions

In this thesis some of the various devices and techniques have been addressed, which have been introduced and studied in the PCI catheterization laboratories over the past decade in order to prevent and treat coronary re-stenosis.

In chapter 1 an introduction is given of the several clinical methods as studied and a brief logistical and historical insight into the organization of these devices in the catheterization laboratory.

In chapter 2 we report on the first clinical results of the RadioCath trial, in which the safety and efficacy of a radioactive liquid filled PCI-balloon was studied. Thirty three patients with a de novo lesion in a native coronary artery were treated with the RadioCath™ device, after successful angioplasty. The average dwell time to deliver a dose of 20 Gy at 0.5 mm into the vessel wall was 418+/-64 seconds. The treatment was well tolerated by most of the patients.
In 79% of them only one inflation cycle was required to deliver the prescribed dose. There were two procedural, device-related complications (5.9%) and three, minor procedural related in-hospital complications (9%). Intracoronary Brachy Therapy using a balloon catheter device, charged with a sodium 186 Re perrhenate solution, seems feasible and safe.

In chapter 3 the 6 month clinical and angiographic follow-up data of the RadioCath trial are presented. Thirty-three patients received 20 Gy 186Re beta-irradiation, immediately after balloon angioplasty. The 6-month restenosis rate was 41% (12/29) and restenosis was located within the target lesion in 8 patients and at the edges of the injured and irradiated segment, outside the target lesion, in 4 patients. At 6 months 4 patients (12%), all stented during the initial procedure, had experienced a late (> 30 days) total occlusion. We concluded that Intracoronary Brachy Therapy of de novo coronary lesions using 186Re is technically safe and feasible, however no reduction in restenosis was observed. The high incidence of late total occlusions may have been prevented by avoiding new stent implantation and prolonging dual antiplatelet therapy.

In chapter 4 we describe the effect of Beta-32P irradiation on Platelet Adhesion to Extracellular Matrix Proteins. In this study, we examined platelet adhesion to 20 Gy Beta-radiation treated extracellular matrix (ECM), fibrinogen, von Willebrand factor, fibonectin and collagen Types III, under flow conditions in a single pass perfusion chamber. Platelet adhesion was quantified by image analysis. 20 Gy Beta-radiation treatment significantly decreased platelet adhesion to vWF and collagen-III and had no effect on adhesion to fibrinogen and fibronectin. The effect on vWF was assessed by measuring the binding of domain-specific antibodies. 20 Gy Beta-radiation treatment affected mostly the A1 (glycoprotein GPI-binding site), A2 and A3 (collagen binding site) domains of vWF but not the D'-D3 (factor VIII, heparin-binding site) and B-C1 (GP-IIb/IIIa-binding site) domains. In conclusion, 20 Gy Beta-radiation treatment can alter the ractivity of certain proteins, in particular von Willebrand factor, resulting in decreased platelet adhesion. The results of this study are a first step in understanding the thrombogenic properties and mechanisms of IVBT with Beta-radiation.

In chapter 5 we report on the results of the Optirad study where a comparison between direct versus delayed ICBT was done in 40 patients presenting with bare metal in-stent restenosis.

The primary objective was the reduction of neointimal hyperplasia by intravascular ultrasound at 6 month follow-up. Secondary objectives were binary restenosis by quantative coronary analysis at 6 month and clinical adverse events at follow-up. Delayed ICBT was safe and feasible although both neointimal hyperplasia and binary restenosis were higher in the delayed treatment arm. No statistical significant difference was found in this small patient population.

In chapter 6 the results of the BEGUT-DES trial are presented. In this study a comparison was made between beta and gamma radiation and DES in patients treated with PCI for a single lesion in a native coronary artery with a re-stenosis after PCI (balloon or stent) and/or type C lesion and/or were on medical treatment for diabetes. The primary endpoint (target vessel failure at 3 years) was observed in a lower proportion of patients

who received DES as compared with ß-BT or γ-BT (15% vs 45% vs 30%). The primary endpoint when comparing ß-BT to γ-BT (30% vs 45%, p=0.34) was in favour of γ-BT, without reaching the level of statistical significance. The results of this study demonstrate a clear long-term benefit of DES over BT, in patients at high risk of restenosis. Considering this outcome DES should be recommended as a first choice revascularization strategy in patients eligible for stent-implantation and at high risk of re-stenosis.

Chapter 7 is based on an editorial published in the European Heart Journal on the different treatment options for coronary in-stent restenosis and compare ICBT versus DES withthe conclusion that in future patients will have to be classified on the basis of biochemical markers of inflammation, genotype, co/morbidity and lesion characteristics to determine the risk of ISR (full) in one individual patient. The outcome of the classification will determine, which therapy is most appropriate where also coronary bypass surgery has to be considered.

In chapter 8 we report on a clinical retrospective comparison on the incidence of stent thrombosis between DES and bare metal stents based on the one-year registry of the Utrecht complication database. In 2005, 1309 patients underwent a PCI procedure with stent implantation. After a median follow-up of 9 months, 1.8% (n = 23) of the patients suffered from stent thrombosis. There were no differences in stent thrombosis rates between DES and BMS (1.4% vs. 1.9%, ns.). This is remarkable since DES were used in more complex and longer lesions. The use of DES in routine daily practice appeared not to be associated with a higher rate of stent thrombosis than BMS based on this analysis.

In chapter 9 we describe the 12 month clinical and 6 month angiographic follow-up of the Custom II study. A multicenter international safety and feasibility trial to evaluate a new revolutionary stent design and delivery system with a biolimus coating on a biodegradable polymer called the Xtent device. This in theory provides in-situ stent length customization and the combined advantages of an initially DES and later a bare metal stent after 9 months due to the biodegradation of the polymer and drug. The CUSTOM-II Trial enrolled 100

patients with de novo lesions in native coronary arteries presenting with either single long lesions (n=69) of > 20 mm length or up to two lesions with a total cumulative anticipated stent length of 60 mm of stent (n=31). Patients were assessed angiographically at 6 months, and clinically at 1 year. Of the 100 patients enrolled, 9 patients experienced a MACE, including five patients whose MACE occurred during index hospitalization (2 NonQ-MI, 2 Q-MI and 1 probable stent thrombosis-related death), and four target lesion revascularizations (TLR), at 6 months. No MACE or stent thrombosis was reported between 6 and 12 months follow-up. In-segment late loss at 6-months was 0.22 ± 0.28 mm, and in-stent late loss had a range of 0.31 ± 0.31 mm. We concluded that The XTENT® customizable stent is clinically safe and efficacious as judged by angiographic and clinical variables through 12 months follow-up.

In chapter 10 we report on a new technique for stenting of coronary bifurcation lesions called the Modified T or Utrech'T ' – technique. Bifurcation lesions occur in more than 20% of coronary interventions. Percutaneous treatment of coronary bifurcation lesions, pose a number of technical challenges to the interventional cardiologist. Each lesion has to be approached with a customized, targeted solution in the context of the clinical picture, anatomy, and pathology. In this report we describe our experience with a new approach for the treatment of bifurcation lesions with a new simplified technique that involves the sequential positioning of two stents, first in the side branch (SB) and second in the main branch (MB). The main aim of this technique is to provide a complete coverage of the bifurcation lesion and of the carina resulting in a relatively small portion of the main branch (MB), only distally to the bifurcation, being scaffolded with a triple layer of stent. In conclusion this study implies that in a preselected population of patients with significant bifurcation lesions, this new approach of modified T stenting with "minimal crush' is technically feasible and showed a low incidence of procedural complications and clinical events after a six months follow-up period.
A practical advantage is that the technique is quite safe and relatively simple to execute. It is therefore a promising strategy that should be added to the current techniques that are being used and evaluated for this purpose, with either bare-metal or drug-eluting-stents.

In chapter 11 we report on the first –worldwide - results of a registry using a Drug Eluting Balloon in the setting of coronary bifurcation lesions. To evaluate short-term safety and efficacy of a drug-eluting balloon (DEB) in patients with bifurcation lesions followed by provisional stenting of the main branch, we set up the DEBIUT Registry. This registry enrolled 20 eligible patients with coronary artery bifurcation lesion. Patients received a PCI with a paclitaxel-coated balloon catheter, followed by provisional stenting of the MB with a bare-metal stent. The procedure was successful in all patients. The use of sequential predilatations with DEB was safe and well tolerated. No acute or subacute closure of side branches occurred after treating with DEB. These encouraging results lead to the organization and start of a multicenter international prospective and randomised study in which three treatment arms are studied for the treatment of coronary bifurcation lesions with the provisional T- technique. Treatment will be with either bare metal stents or normal balloon predilatation versus bare metal stent and drug eluting balloon prediltation versus drug eluting stents and normal balloon prediltation. In total 120 patients will be enrolled. Hopefully the first angiographic and clinical results will be known early 2010.

In chapter 12 we report on the clinical results of a new modern thin strut cobalt chromium stent. In 712 patients treated at the UMC Utrecht with PCI for ischemic coronary artery disease we describe the clinical restenosis rate and adverse events during 12 month follow-up. We conclude that based on a simple triage in which patients without an indication for DES according to our descision module, the clinical safety and efficacy with this modern bare metal stent is very good.

Final comments

During the past two decades, the percutaneous treatment (PCI) for ischemic coronary disease by balloon and/or stents has taken a major leap. As compared to CABG this treatment modality is easy accessible, less invasive and can be performed very safe. Even if compared to minimal invasive surgery, the simple single-needle access site required for PCI can hardly be beaten in its simplicity. The biggest drawback compared with CABG is the higher recurrence of restenosis and therefore repeat revascularization

procedures. Although most patients still prefer the less invasive procedure (certainly in the non-western world), and accept the risk of potential re-do procedures, there is a need to try to prevent, but also to improve treatment of restenosis. In order to achieve the best possible angiographic and clinical outcome, one has to differentiate between *treatment* and *prevention* of coronary restenosis.

For the *treatment* of restenosis once it has occurred several therapies are discussed. Intracoronary Brachytherapy (ICBT) has been described and might probably have a value and place still, however due to the concomitant logistical issues will never be used on a large scale relative to DES and/ or DEB. Currently re-PCI with a DES or CABG are the best proven options once (in-stent-) restenosis occurs.

Prevention, by trying to cause as little damage as possible to the coronary artery wall during PCI and thus avoiding activating restenotic triggers. Modified bifurcation PCI techniques and the clinical impact of new generation thin-strut stents and new generation DES with biodegradable polymers have been discussed in this thesis. Meanwhile local drug delivery with a single or multiple agents such as a drug eluting stent (DES) or balloon (DEB) can be potentially very helpful in further suppression of the activation of (sub-) acute restenotic triggers such as chronic inflammation and excessive wound healing of the arterial vessel wall. The latter is still relatively new and has proven itself so far for (bare-metal) in-stent restenosis but might have more future indications. For instance, bifurcation lesions, small vessels and vulnerable plaques. Less stent material could be an advantage in comparison to the use of DES, without the necessity of long-term dual antiplatelet therapy. DES is of course a well proven concept, however resenosis still occurs and questonmarks are raised concerning long-term safety of DES.

The most ideal product for PCI in near future could be a complete bioabsorbable stent which prevents early recoil and treats dissections after and during PCI and prevents restenosis by combining several anti-inflammatory and anti-proliferative drugs on its surface. By the nature of its complete absorption of the device, this could lead to a broader

indication for PCI (small/distal vessels) and more re-PCI's since the limitation of putting layer on layer of metal within the coronary artery will have been solved. The technical challenges of combining these properties into an 'easy to use' stent-design proves to be enormous and might take several more years to overcome.

It is however very unlikely that just one single process is responsible for the occurrence of restenosis. The whole process is probably the result of many different stimuli in combination with other – external ?- factors. Therefore it is necessary to have different approaches for different clinical scenarios and situations. In future we might have the choice of specific anti-inflammatory, anti-proliferative, anti-migratory and pro-endothelial healing balloon or stent devices, each designed for a specific patient sub selection. Potentially in combination with simple systemic drugs taken orally. This brings us the challenge of better understanding the different mechanisms and interactions within the re-stenotic cascade and calls for specific diagnostic tools ideally diagnosed by a simple blood test. Results of the installed Biomark data bank at the department of experimental cardiology could help in better understanding and tailoring our therapy of choice and in the end provide a better result for our patients.

Nederlandse Samenvatting en Conclusies

In dit proefschrift zijn verschillende modaliteiten en technieken besproken die gedurende het afgelopen decennium onderwerp zijn geweest van studies op de hartkatheterisatiekamerd te Utrecht, ter behandeling en preventie van coronaire re-stenosering.

In hoofdstuk 1 is een introductie gegeven over de verschillende bestudeerde kinische methodes en is een kort historisch overzicht gegeven ten aanzien van de logistieke consequenties van het gebruik van deze modaliteiten in de catheterisatie-afdeling.

In hoofdstuk 2 worden de klinische resultaten beschreven van de RadioCath studie waarbij de veiligheid en effectiviteit van een vloeibare radio-actief gevulde PCI-ballon werd onderzocht. Drie en dertig patienten met een de novo laesie in een natief coronairvat werden behandeld met het RadioCath™ device direct na succevolle PCI procedure. De gemiddelde bestralingsrijd om een dosis van 20 Gy op 0.5 mm in de vaatwand af te genven bedroeg 418 +/- 64 seconden. De behandeling werd goed verdragen door de meeste patienten. In 79% was slechts een inflatie nodig om de voorgeschreven dosis af te geven. Er worden twee peri-procedurele, device-gerelateerde complicaties beschreven (5.9%) en drie minder ernstige complicaties tijdens ziekenhuis opname (9%). Intracoronaire Brachytherapie met een PCI-ballon gevuld met 186 Rheniumpherrenate blijkt uitvoerbaar en veilig.

In hoofdstuk 3 worden de 6 maands klinische en angiografische resultaten van de RadioCath studie gepresenteerd. Drie en dertig patiënten met een de novo laesie in een natief coronairvat werden behandeld met het RadioCath™ device direct na succesvolle PCI procedure. De 6 maands restenose ratio bedraagt 41% (12/29), waarbij restenose zich bij 8 patiënten binnen het behandelde segment en op de grenzen bevond. Bij 4 patiënten wordt restenose buiten het behandelde segment gevonden. Bij vier patiënten (12%), allen behandeld met een stent tijdens de index-procedure, wordt een late (>30 dagen) totale occlusie gevonden. Wij concluderen dat intracoronoraire brachytherapie van de novo coronaire stenose met een 186 Re gevulde ballon weliswaar uitvoerbaar en veilig is,

echter er wordt geen aantoonbare reductie van restenose gevonden. De hoge incidentie van late totale occlusies had wellicht voorkomen kunnen worden door stent implantatie te vermijden en langduriger combinatie antistollingspreparaten voor te schrijven.

In hoofdstuk 4 wordt het effect van 32P Beta straling op bloedplaatjes adhesie aan extracellulaire matrix proteines beschreven. Plaatjes adhesie in een single-pass perfusie model, gedurende bèta straling met een dosis van 20Gy, aan extracellulaire matrix, fibrinogeen, van Willebrand factor, fibronectine en type III collageen wordt beschreven. Plaatjes adhesie werd gekwantificeerd door beeld analyse. Straling met een dosis van 20Gy, 32P verminderde significant de adhesie van plaatjes aan vWF en type II collageen, maar had geen effect op adhesie aan fibrinogeen en fibronectine. Het effect op vWF werd gemeten door binding activatie van specifieke antilichamen. De bètastraling met 20Gy, beïnvloedt met name de A1 (glycoproteine zijde), A2 en A3 (collageen zijde) van VWF, maar niet de D1-D3 (factor VIII, heparine binding zijde) en B-C1 (GP IIb/IIIa binding) domeinen. In conclusie blijkt dat bèta straling met 20Gy- 32P, de reactiviteit van sommige proteines kan veranderen, met name VWF, waardoor een verminderde plaatjes adhesie optreedt. De resultaten van deze studie zijn een eerste stap in het onderzoek naar de thrombogene eigenschappen van intravasculaire brachytherapie met bètastraling.

In hoofdstuk 5 worden de 6 maands angiografische en 2 jaars klinische resultaten van de Optirad studie beschreven. Hierbij werd het verschil tussen directe en verlate bestraling onderzocht bij 40 patiënten behandeld voor (bare-metal) in stent restenose. Primair eindpunt was de reductie van neointima hyperplasie met IVUS bij 6 maands follow-up. Secundaire uitkomstmaten waren angiografische restenose na 6 maanden en klinische adverse events gedurende follow-up. Verlate brachytherapie blijkt uitvoerbaar en veilig, echter zowel neointima hyperplasie als angiografische restenose is hoger in de verlate behandel arm.
In deze kleine studie groep werd echter geen significant verschil tussen beide armen gevonden.

In hoofdstuk 6 worden de resultaten van de BEGUT-DES studie weergegeven. In deze studie wordt een vergelijk tussen bèta en gamma straling en DES onderzocht bij patiënten met een hoge kans op restenose. Patiënten verwezen voor PCI van een single-laesie in een natief coronairvat met re-stenose na eerdere PCI (stent of ballon), en/of een type C laesie, en/of onder medicamenteuze behandeling voor diabetes werden geincludeerd. Het primaire eindpunt (target vessel failure na drie jaren), is lager bij de DES groep vergeleken met bèta of gamma-BT (15% vs 45% vs 30%). Onderling vergelijk tussen beide stralingsbronnen laat een betere primaire uitkomst zien voor gamma-BT (30 vs 45 %, p=0.34),echter zonder statistische significantie. De uitkomsten van deze studie tonen een duidelijk beter resultaat voor DES versus intracoronaire bestraling bij patiënten met een hoge kans op restenose. DES zou dan ook de voorkeurstherapie moeten zijn bij deze patiënten selectie.

In hoofdstuk 7 worden de verschillende behandelings vormen voor coronaire restenose beschreven en wordt ICBT met DES gebruik vergeleken. Geconcludeerd wordt dat in de toekomst patiënten stratificatie ter evaluatie van risico voor restenose op basis van verschillende parameters zoals biomarkers voor inflammatie, genotype en co-morbiditeiten gedaan zal moeten worden. Op basis van uitkomsten van deze parameters zal een behandel vorm gekozen moeten worden waarbij onder andere ook bypass chirurgie.

In hoofdstuk 8 wordt het verschil in klinische optreden van in-stent thrombose tussen bare metal en drug eluting stents beschreven bij alle patiënten die een PCI met stent kregen in het UMCU. Het betreft hier een retrospectieve analyse van onze eigen database. In 2005 werden 1309 patiënten gedotterd met stentimplantatie in het UMCUtrecht. Bij een gemiddelde follow-up van 9 maanden werd bij 23 patiënten (1.8%) een stent thrombose gemeld. Er werd geen verschil tussen BMS en DES beschreven (1.4% vs 1.9%, =ns.). Dit is des te opmerkelijker daar DES in een hoger risico patiënten categorie werd gebruikt dan BMS. OP basis van deze analyse, is het gebruik van DES in de dagelijkse routine praktijk zoals in UMCU niet geassocieerd met een hoger risico op het optreden van stent thrombose.

In hoofdstuk 9 worden de 6 maands angiografische en 1 jaars klinische uitkomsten van de Custom II studie weergegeven. Het betreft een internationale multi-center studie naar veiligheid en effectiviteit van een revolutionair nieuw stent systeem met een Biolomus A9 coating op een biodegradable polymeer; het Xtent© Custom NX™ systeem. Het device combineert de mogelijkheid tot in-situ (in het coronairvat) stentlengte keuze met de initiële voordelen van een DES zonder de late nadelen doordat medicijn coating en polymeer na een periode van 9 maanden zijn opgelost. In totaal werden 100 patiënten geincludeerd in de CustomII studie met de novo coronair stenose. Het betrof hier ofwel 1 lang letsel van > 20 mm (n=69), ofwel twee laesies's met een lengte van in totaal maximaal 60 mm (n=31). Gedurende de follow-up werd bij 9 patiënten een major adverse event gerapporteerd waarvan 5 al tijdens de indexbehandeling optraden (4 infarct en 1 overlijden) en 4 ten gevolge van re-PCI bij 6 maands follow-up. Er werden geen adverse events tussen 6 en 12 maands follow-up gevonden. In behandelde segment late-loss was 0.22 +/- 0.28 mm, en in stent late-loss was 0.31 +/- 0.31 mm. De conclusie is dat het Xtent device veilig en effectief is gebleken gedurende 12 maands follow-up.

In hoofdstuk 10 wordt een nieuwe stent techniek voor coronaire bifurcatie letsels beschreven genaamd Modified T of Utrech'T' techniek. Het aandeel van coronaire bifurcatie letsels in de dagelijkse PCI praktijk bedraagt ongeveer 20%. Het betreft hier een technisch uitdagende patiënten populatie voor de dotteraar, waarbij elke bifurcatie in de juiste context van anatomie en pathologie moet worden benaderd en behandeld. In deze beschrijvende analyse wordt een nieuwe vereenvoudigde techniek beschreven waarbij altijd twee stents worden gebruikt in achtereenvolgens de zijtak en hoofdtak van de bifurcatie. Het belangrijkste doel is om hierdoor altijd een volledige bedekking van het ostium van de zijtak met stent struts te bereiken zonder overtollige overlap van stent metaal in de hoofdtak. Alleen distaal bij de carina wordt een zone van mini-crush gedaan. Bij patiënten met een geschikte bifurcatie anatomie voor deze benadering werd gedurende zes maands klinische follow-up een goede veiligheid en effectiviteit van deze techniek gevonden. Het grote voordeel is dat deze techniek de bifurcatie procedure sterk vereenvoudigt en met zowel bare-metal als DES gebruikt kan worden.

In hoofdstuk 11 wordt een eerste wereldwijd gepubliceerde studie beschreven naar het gebruik van een Drug Eluting Ballon (DEB) bij de behandeling van bifurcatie letsels. De opzet van de DEBIUT –registry wordt beschreven waarbij 20 patiënten met coronaire bifurcatie letsels worden behandeld met een provisional T stent techniek na sequentiele predilatatie met DEB. De procedure was succesvol in alle patiënten en gedurende 4 maands klinische follow-up werden geen nadelige effecten gerapporteerd. Deze uitkomsten hebben inmiddels geleid tot het opzetten van een multicenter prospectief gerandomiseerde studie (DEBIUT), waarbij 120 patiënten zullen worden geincludeerd en angiografisch en klinisch vervolgd. Eerste resultaten worden eind 2010 verwacht.

In hoofdstuk 12 worden de resultaten van de Skylor Registry beschreven. De klinische uitkomsten van 712 patiënten (800 stents), behandeld met een nieuwe dunne bare metal cobalt chromium stent worden middels een retrospectieve data analyse gerapporteerd. Gedurende een 12 maands follow-up wordt in een geselecteerde patiënten populatie –zonder DES indicatie- een goede veiligheid en effectiviteit van deze nieuwe stent beschreven. De beslisboom tot DES vs. Bare Metal Stent indicatie in UMCUtrecht wordt beschreven. In conclusie kan op basis hiervan met deze nieuwe generatie stents een goed en veilig klinisch resultaat bereikt worden bij een geselecteerde patiënten populatie.

Slot opmerkingen

Gedurende de afgelopen twee decennia heeft de percutane behandeling van obstuctief coronarialijden middels PCI een enorme vlucht genomen. Vergeleken met CABG is deze behandelingsmethode makkelijk en veilig toepasbaar en veel minder invasief. Zelfs vergeleken met minimaal invasieve chirurgische technieken is het voor wat betreft bovenstaande moeilijk om de 1 naald techniek te verslaan. Het grootse nadeel vergeleken met CABG is echter nog altijd het hogere percentage restenose waarvoor opnieuw revascularisatie noodzakelijk is. Omdat desondanks de meeste patiënten (zeker in de niet Westerse Wereld) deze weinig invasieve behandelings vorm verkiezen, bestaat er een noodzaak tot niet alleen restenose preventie, maar ook betere behandeling ervan. Om uiteindelijk het beste angiografische en klinische resultaat te bereiken moet er onderscheid worden gemaakt tussen *behandeling en preventie*.

Voor de *behandeling* van reeds ontstane restenose zijn verschillende therapieën besproken. De rol van Intracoronaire Brachytherapie is uitvoerig besproken, en wellicht nog steeds valide, echter door logistieke problemen die deze behandelingsvorm met zich meebrengt niet zo makkelijk toepasbaar als een DES of DEB. Momenteel zijn re-PCI met een DES of CABG de twee enige bewezen effectieve behandel methodes indien zich een (stent-) restenose voordoet.

Preventie, door zo min mogelijk traumatisch te werken op de vaatwand tijdens de PCI waardoor uiteindelijk minder prikkels zullen ontstaan die de restenose op gang kunnen brengen. Gemodificeerde bifurcatie procedures en het gebruik van nieuwe thin strut stents en nieuwe DES met biodegradable polymeren zijn hier besproken in dit proefschrift. Daarnaast kan door locale medicatie toediening op de plaats van de stenose, zoals met de drug eluting ballon, potentieel de activatie van prikkels voor excessieve re-endothelialisatie onderdrukt worden. De laatste methode is relatief nieuw en heeft zichzelf tot dusver alleen voor in-stent restenose bewezen, maar heeft wellicht meer indicaties als bifurcaties, kleine vaten en onstabiele plaques. Het ontbreken van stentmateriaal, en daarmee samenhangende indicatie voor langdurige antistollings-medicatie, zou een groot voordeel ten opzichte van DES kunnen zijn. Uiteraard heeft ook de DES zich in dit opzicht bewezen, echter desondanks blijft toch restenose optreden en zijn er potentieel nadelige lange termijn effecten samenhangend met de combinatie van medicatie en polymeren op de huidige generatie DES.

In de toekomst zou het ideale product voor PCI een compleet absorbeerbare stent kunnen zijn, die vroege complicaties als recoil (terugveren van de vaatwand) en dissecties goed kan voorkomen en behandelen, en door een combinatie coating met verschillende anti-inflammatoire en anti-proliferatieve medicijnen ook geen restenose meer heeft. Door deze eigenschappen zou de indicatie voor PCI zich kunnen uitbreiden doordat kleinere en distale vaten worden behandeld (nu 'niet de moeite waard') en het bezwaar van re-PCI waarbij metaal in metaal wordt geplaatst wordt voorkomen. Dit is weliswaar zo gezegd maar niet zo gedaan. De technische problemen bij het combineren van deze

eigenschappen met het behoud van de gebruiksvriendelijkheid van de huidige generatie stents zijn groot en zal nog enige jaren ontwikkeling en onderzoek vergen.

Aangezien echter het hele restenose proces een combinatie is van verschillende stimuli met daarbij externe factoren is het hoogst onwaarschijnlijk dat de preventie in een behandelingsvorm geboden kan worden. Zeer waarschijnlijk zullen in de toekomst verschillende behandelingsvormen, gericht op verschillende scenario's ontwikkeld worden, waarbij een keuze tussen anti-inflammatoire, anti-proliferatieve, anti-migratie en pro-endothelialisatie ballon of stent devices zal bestaan. Mogelijk in combinatie met orale toegepaste medicatie.
Dit brengt ons de uitdaging om de verschillende uitlokkende factoren voor restenose beter te begrijpen en middels simpele toepasbare diagnostiek als bloedonderzoek te onderzoeken. In de toekomst zullen de resultaten van onderzoek door de Biomark data bank zoals recent geïnstalleerd op onze afdeling experimentele cardiologie van groot belang zijn om onze verschillende behandelingsmodaliteiten nog beter toe te kunnen passen en zodoende een beter resultaat voor onze patiënten te bereiken.

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CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 11 oktober 1961 te Addis Abeba-Ethiopie. In 1979 werd het eindexamen VWO behaald, waarna in 1981 na twee jaren Fysische Geografie studie aan de Vrije Universiteit te Amsterdam met de studie Geneeskunde werd begonnen. In september 1988 werd het arts diploma behaald en direct gestart met werk als arts-assistent Neurologie in het Spaarne Ziekenhuis Heemstede (Dr.R.Groen). In 1989 gevolgd door een functie als arts-assistent Cardiologie in het OLVG te Amsterdam waarna in 1990 een toezegging tot opleiding plaats werd verkregen. Er volgde hierop een B-jaar Cardiologie en 2 jaren Interne Geneeskunde in het Kennemer Gasthuis te Haarlem (opleiders Dr. G. Kan en A. Hensen). Tussen 1994 en 1997 werd de opleiding tot algemeen cardioloog afgerond in het OLVG te Amsterdam (opleider Dr. R. Schuilenburg). Tijdens de opleiding was hij actief als bestuurslid (1993-1996) binnen de NVVC als voorzitter Juniorkamer. Gedurende de opleiding ontstond er een sterke belangstelling voor de Interventie Cardiologie. In februari 1997 begon hij als fellow-Interventie Cardiologie in het UMC Utrecht, waar hij 2001 toetrad tot de toenmalige HLCU Maatschap. Naast de klinische werkzaamheden als staflid interventie cardiologie en medisch hoofd van de hartkatheterisatiekamers, houdt hij zich met name bezig met organisatie en leiding van de afdeling klinische R&D van de Cardiologie. Deze houdt zich naast medicijn onderzoek met name bezig met (nieuwe) stent en ICD device studies.

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PRESENTATIONS

***Transradial PCI*:** Stenting on an Outpatient Basis; Scientific Sessions of the American Heart Association, Dallas,1994 / Transradial Artery Occlusion after Transradial Coronary Angioplasty; Scientific Sessions of the American Heart Association, Anaheim,1995 / Internnational Transradial Stent Course, ADIC, Amsterdam,1996 / Dutch Society of Cardiology, 1996 / Dutch Working Councel of Cardiology, 1995 / TCT, Washington,1996 / ESC-Birmingham, 1996.

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Drug Eluting Balloon; TCT 2007-Washington D.C., CSI India-2007 Hyderabad, JIM 2008-Rome, CIT 2008-Beijing, PCR 2008- Barcelona, EBC 2008-Prague, TCT 2008-Washington D.C., JIM 2009-Rome, CIT 2009-Beijing, Euro PCR 2009

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