Clinical evaluation of radioactive stents

Klinische evaluatie van radioactieve stents

PROEFSCHRIFT

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Chapter 1

Introduction.

Overview of the Thesis

Restenosis, the major problem after stent implantation, is caused by in-stent neointimal hyperplasia. A number of methods and techniques have been studied during the last ten years to address this issue, but in-stent restenosis has remained at a rate of 15-25% in most of the clinical trials. Several experimental and clinical trials showed that brachytherapy, following a balloon angioplasty or stent implantation, reduced restenosis by inhibiting neointimal hyperplasia. Several in-vitro experiments and animal studies demonstrated a reduction of in-stent restenosis after the implantation of ^{32}P β-particle emitting radioactive stents.

The research objective of this thesis was to evaluate whether the implantation of radioactive stents in patients with coronary artery disease could reduce in-stent restenosis. In order for radioactive stents to become an accepted treatment in the current clinical practice its safety, feasibility, efficacy, mechanism of action, and side effects needed to be investigated.

In the first part of the thesis (chapter 2), the concept of intracoronary brachytherapy is discussed. It also includes the rationale, historical development, radiation physics, radiobiology, devices and isotopes used, dosimetry, limitations, safety issues, indications, contraindications, and an overview of several of the undertaken brachytherapy trials.

In the second part of the thesis (chapters 3 & 4), the results of the trials concerning the safety, feasibility and effective treatment dose are presented to describe the indication and the therapeutic range of radioactive stent implantation.

The third part of the thesis (chapters 5-7) describes the mechanisms of restenosis inhibition by radioactive stents and the side effects observed in the clinical trials.

The fourth part of the thesis (chapters 8-10) provides the results of the trials, which were conducted to prevent edge restenosis, which occurs frequently after radioactive stent implantation. The following treatments were included: a) stents with Cold Ends - radioactive stents extended with non-radioactive parts, b) stents with Hot Ends - stents in which both ends are made more radioactive than the center part, and c) use of square shouldered balloons to implant radioactive stents.

The fifth part of the thesis (chapter 11) is based on an intermediate term follow-up study. This trial investigated the angiographic result 12 months after the implantation of radioactive stents.

The overall aim of this thesis was to evaluate the suitability of radioactive stents to control restenosis by conducting appropriate clinical trials.

Part 1

The concept of intracoronary brachytherapy.

Chapter 2

Intracoronary Brachytherapy: A new treatment for the prevention of restenosis.

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Intracoronary brachytherapy: a new treatment for the prevention of restenosis

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Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is an accepted treatment for coronary artery disease.[1] However, angiographical restenosis is reported in 30–60% of patients after a successful PTCA.[1–3] The main mechanisms of restenosis include acute elastic recoil of the vessel, late constriction of the arterial wall (negative remodeling), and neointimal hyperplasia.[4–8] Neointimal hyperplasia develops by migration and proliferation of smooth muscle cells and myofibroblasts after balloon-induced trauma of the arterial wall and by deposition of an extracellular matrix by the smooth muscle cells.[7,9–11] The restenosis rate has been reduced to 15–20% by stent implantation,[3,12] by preventing elastic recoil and negative remodeling.[13] However, the occurrence of restenosis after stent implantation remains unresolved, especially in small vessels and long lesions, where it may take place in more than 30% of the cases.[14] It is primarily caused by neointimal hyperplasia, which occurs due to trauma of the arterial wall by the stent struts.[6] The treatment of in-stent restenosis with conventional techniques (balloon angioplasty or debulking) is rather disappointing, with restenosis rates of 27–63%, which increase with the number of re-interventions.[15–19] The term brachytherapy is used to describe intracavitary or interstitial radiation therapy.[20] Recently, the term vascular brachytherapy has been introduced to describe endovascular radiation therapy. Vascular brachytherapy with a radioactive source after PTCA or stent implantation is a promising treatment that might reduce restenosis by inhibition of neointimal hyperplasia[21–23] and constrictive remodeling[24,25] after percutaneous intervention.

Rationale

Radiotherapy can successfully treat hypertrophic scars, keloids, heterotopic bone formation after total hip replacement, ophthalmic pterygia and solid malignancies. Usually, radiation doses of 7–10 Gy are used to treat these benign diseases, thereby efficiently inhibiting fibroblastic activity without influencing the normal healing process, and without causing significant morbidity during long-term follow-ups of up to 20 years.[26–28] Vascular brachytherapy, using radiation doses of 12–20 Gy, appears to be efficacious in preventing restenosis by inhibiting neointimal formation[22,29–31] and by increasing lumen diameters (positive remodeling).[22,32–34]

History

In 1964, Friedman[35] reported on the first in vivo use of intravascular radiotherapy. The first clinical trial, treating 30 patients with gamma (^{192}Ir) endovascular radiotherapy for the treatment of in-stent restenosis of femoropopliteal arteries, was started in 1990 by Liermann.[23] A reduced restenosis rate was observed without short- or long-term (5-year follow-up) complications. In

1995, Popowski[36] reported on the first centering catheter, used in vascular brachytherapy with beta radiation to give a more homogeneous dose distribution to the vessel wall. In 1997, Condado[37] treated 21 patients with de novo coronary lesions with angioplasty followed by intracoronary brachytherapy, using ^{192}Ir. A restenosis rate of 27% was observed at 6-month follow-up. Also, due to the high prescribed dose, the first occurrence of a pseudoaneurysm after vascular brachytherapy was reported. Later in 1997, Teirstein[38] reported on the first randomized double-blind placebo-controlled intracoronary brachytherapy trial, showing safety and efficacy of gamma (^{192}Ir) radiation for the treatment of in-stent restenosis.

Currently, multiple brachytherapy trials are either completed, ongoing or will be started shortly. An overview of brachytherapy trials is given in Table 1.1.

Physics

Radioactivity is the process in which an unstable nucleus, which has either too many or too few neutrons, changes to a stable state (ground state). When it reaches the stable state, the basic element itself has changed, and this is known as radioactive disintegration or radioactive decay. The stable state is reached by α-particle emission, β-particle emission or electron capture (Figure 1.1). α-Particles are heavyweight charged particles which can travel very short distances within tissues. β-Particles are lightweight high-energy electrons, with either positive or negative charge. When β-particles, which can travel only finite distances within tissues, are slowed down by nuclear interactions, they give rise to high-penetration X-rays, called Bremsstrahlung. γ-Rays are photons originating from the center of the nucleus, and take the form of electromagnetic radiation. Most often, an unstable nucleus will emit an α- or β-particle followed by γ-radiation. Only a few radioisotopes, e.g. phosphorus-32 (a pure β-emitter) emit particles without γ-radiation. γ-Rays may have either one or two discrete energy values or a broad spectrum of many energy values. They penetrate deeply within tissues.[39-41]

When reaching a stable state by electron capture, the nucleus captures an electron from the innermost (closest to the nucleus) orbit, thereby making the outer shell with electrons unstable. To fill the gap left by the captured electrons, electrons from the outer orbit jump to the innermost orbit, which also leads to the emission of photons, called X-rays, which take the form of electromagnetic waves. γ-Rays and X-rays are both high-energy photons, without charge or mass. The only difference between γ-rays and X-rays is in their origin. Visible light waves and radiowaves are low-energy photons.[39]

Radiobiology

When radiation is absorbed in a tissue, it can either cause direct damage to a critical target by ionization or it can indirectly damage a critical target by interacting with other molecules to produce free radicals, which will subsequently damage the critical target. Approximately 80% of the radiation damage is caused by these free radicals. Clearly, the most critical target that could be damaged by radiation is DNA. A consequence of this damage is that the cell will lose its ability to proliferate, which will ultimately lead to its death. Early and late toxic effects in normal tissue are mainly caused by cell death.[39,42]

There are several hypotheses explaining how radiation therapy could inhibit neointimal proliferation and thereby prevent restenosis:

- Radiation might cause the inactivation of all target smooth muscle cells and myofibroblasts, while the surviving endothelial cells would repopulate and reline the artery. If this is true, smooth muscle cells should be more radiosensitive than endothelial cells. However, experimental evidence suggests no differences in the radiosensitivity of smooth muscle cells and endothelial cells.[31,43]

Study	No. of patients	Dose (Gy)	Lesion criteria	Lesion length (mm)	Source	Sponsor
ARREST	50	<8, <35[a]	De novo	≤25	^{192}Ir	Vascular therapies
ARTISTIC	50	12, 15, 18[b]	In-stent restenosis	≤25	^{192}Ir	Vascular therapies
BERT	20	12, 14, 16[c]	De novo	≤15	Sr/^{90}Y	Novoste
BERT 1.5	31	12, 14, 16[b]	De novo	<20	Sr/^{90}Y	Novoste
Betacath	1456	0, 14, 18[b]	De novo, restenotic	<20	Sr/^{90}Y	Novoste
BetaWRIST	50	20.6[d]	Instent restenosis	≤47	^{90}Y	Boston Scientific
BETTER	150	20[d]	De novo, restenotic	≤25	^{32}P	Radiance
BRIDGE	100	0, 20[c]	De novo	≤15	^{32}P	Guidant
BRIE	13	14, 18[b]	De novo, restenotic	<20	Sr/^{90}Y	Novoste
Compassionate use Rotterdam	22	16, 20[b]	In-stent restenosis	<30	Sr/^{90}Y	Novoste
CURE	30	20[e]	De novo	<22	^{188}Re	Columbia University
Dose Finding	181	9, 12, 15, 18[d]	De novo	<15	^{90}Y	Schneider
GAMMA-1	252	0, 8–30[f]	In-stent restenosis	≤45	^{192}Ir	Cordis
GAMMA-2	125	14[b]	In-stent restenosis	≤45	^{192}Ir	Cordis
GAMMA-3	280	14[b]	In-stent restenosis	≤45	^{192}Ir	Cordis
Geneva	15	18[d]	De novo	<29	^{90}Y	Schneider
GRANITE	100	14[g]	In-stent restenosis	≤45	^{192}Ir	Cordis
INDIRA	800	0, 11[a]	De novo, in-stent restenosis	≤30	^{192}Ir	Cordis
INHIBIT	360	0, 20[c]	In-stent restenosis	<44	^{32}P	Guidant
IRIS	37	5–12[h]	De novo, restenotic	<28	^{32}P	Isostent
LongWRIST	120	0, 15[b]	In-stent restenosis	>80	^{192}Ir	Cordis
MARS	35	20 Gy[c]	De novo	<20	^{188}Re	Mallinckrodt
PERTH	100	18[d]	In-stent restenosis	20–80	^{188}Re	Royal Perth Hospital
PREVENT	37	0, 28, 35, 42[c]	De novo, restenotic, In-stent restenosis	<22	^{32}P	Guidant
P32 Dose Response	162	45–92[h]	De novo, restenotic, In-stent restenosis	<28	^{32}P	Isostent
P32 Dose Response Cold Ends	50	22–92[h]	De novo, restenotic	<15	^{32}P	Isostent
P32 Dose Response Hot Ends	50	71–126[h]	De novo, restenotic	<15	^{32}P	Isostent
Radiation Stent Safety Trial	30	52–106[h]	De novo, restenotic	<13	^{32}P	ACS
RENO	1000	14–20[b] 16–22[b]	De novo, restenotic, In-stent restenosis	Not limited	Sr/^{90}Y	Novoste
SCRIPPS-1	55	0, 8–30[f]	Restenotic	<30	^{192}Ir	Cordis
SCRIPPS-2	100	0, 8–30[f]	In-stent restenosis	<65	^{192}IR	Cordis
SCRIPPS-3	500	0, 14[b]	In-stent restenosis	<81	^{192}Ir	Cordis
SMARTS	180	12[g]	De novo	≤25	^{192}Ir	Vascular therapies
START	476	0, 16, 20[b]	In-stent restenosis	<20	Sr/^{90}Y	Novoste
START 40/20	206	16, 20[b]	In-stent restenosis	<20	Sr/^{90}Y	Novoste
SVG WRIST	120	0, 15[b]	SVG	≤45	^{192}Ir	Cordis
Venezuela	21	19–55[f]	De novo, restenotic	<30	^{192}Ir	Non-commercial
WRIST	130	0, 15[b]	In-stent restenosis	≤47	^{192}Ir	Cordis

[a] With intravascular ultrasound guidance. [b] At 2 mm from the source. [c] At 0.5 mm into the vessel wall. [d] At 1 mm from balloon surface. [e] At media. [f] To EEM. [g] At 3 mm from the source. [h] Cumulative dose over 100 days delivered to 1-mm depth outside the stent surface. [i] At 1.5 mm from the source.

Table 1.1
Intracoronary brachytherapy trials.

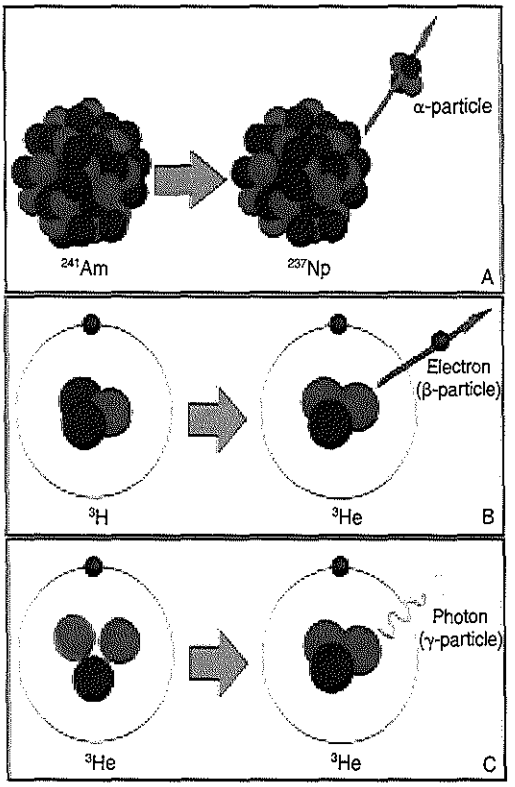


Figure 1.1
Production of radioactivity.
(A) Example of α-radiation: unstable nuclear core (left illustration) turns into a stable core by emitting an α-particle (right illustration).
(B) Example of β-radiation: unstable nuclear core (left illustration) turns into a stable core by emitting a β-particle (right illustration).
(C) Example of γ-radiation: unstable nuclear core (left illustration) turns into a stable core by emitting a γ-particle (right illustration).

- Radiation could cause a large amount of potentially proliferating and migrating smooth muscle cells to either lose their ability to proliferate or to perish. In this way, the remaining proliferating cells are too few to cause restenosis, especially when taking into account the fact that cells have a finite proliferative capacity.[44] What can be learned from previous trials is that doses of more than 20 Gy are required to completely eliminate the smooth muscle cell population, which could result in late complications (e.g. the development of aneurysms).[31,37,38]
- Lower doses (<20 Gy) are less likely to result in late complications. Consequently, restenosis may only be delayed for the period of time necessary for the population of smooth muscle cells to regenerate. If this were true, a delayed restenosis of 1–3 years would be expected.[31] Additional evidence for this theory comes from a clinical trial[23] where 12 Gy was prescribed to prevent restenosis in femoral arteries. No stenoses were seen after 3–27 months of follow-up;[45] however, 16% restenosis was seen after prolonged follow-up.[46]

Brachytherapy devices and used isotopes

Vascular brachytherapy can be performed by catheter-based systems, radiation balloons (both high dose rate) or radioactive stents (low dose rate). Among high-dose-γ-emitting rate devices are (^{192}Ir) or β-emitting (^{32}P, ^{90}Sr, ^{90}Y) seeds or wires and temporary filling of a dilatation balloon catheter with a high-activity β-emitting solution (radionuclide liquid ^{188}Re or ^{186}Re) or ^{133}xenon gas.[40] For an overview of the brachytherapy devices currently used in patients, see Table 1.2. For an overview of the used isotopes, see Table 1.3.

Dosimetry

Vascular brachytherapy requires accurate knowledge of the dose delivered at 0.5–5 mm from the radioactive source. The treated coronary artery segment is ±2–5 cm in length, with a diameter of 3–5 mm and a vessel wall thickness of 0.5–3 mm. The radiation dose given to the vessel wall should probably target the media as well as the adventitia.[40,47,48]

Radiation device	*Manufacturer*	*Source information*		*Delivery*	*Centering*
The ^{192}Ir Radioactive seed ribbon	Best Medical International/Cordis	^{192}Ir	Seed ribbon	Manual	No
Angiorad System	Vascular Therapies	^{192}Ir	Wire	Manual	No
Solution-Applied Beta Emitting Radioisotope (SABER) System	Columbia University	^{188}Re	Liquid-filled balloon	Manual	Yes
Beta-Cath System	Novoste	Sr/^{90}Y	Seeds	Hydraulic	Yes
Nucletron Coronary System	Nucletron/Guidant	^{32}P	Wire	Afterloader	Yes
Galileo System	Guidant	^{32}P	Wire	Afterloader	Yes
Isolated Liquid Beta Source Balloon Radiation Delivery System	Radiant	^{188}Re	Liquid-filled balloon	Manual	Yes
Multi-link RX Radiation Coronary Stent System	ACS	^{32}P	Stent	Manual	Yes
Schneider–Sauerwein Intravascular Radiation System	Schneider/Boston Scientific	^{90}Y	Wire	Afterloader	Yes
Soft X-ray System	Interventional Innovations Corporation	X-ray	X-ray device	Automated	No
Beta-stent	Isostent	^{32}P	Stent	Manual	Yes
RDX Radiation Delivery System	Radiance	^{32}P	Balloon	Manual	Yes
Gamma IRT Delivery System	Cordis	^{192}Ir	Seeds	Manual	No
Liquid-filled balloon	Mallinckrodt	^{186}Re	Liquid-filled balloon	Manual	Yes

Table 1.2
Brachytherapy devices.

Isotope	Emission	Maximum energy	Half-life
^{192}Ir	γ	612 keV	74 days
$^{90}Sr/^{90}Y$	β	2.28 MeV	28.6 years
^{90}Y	β	2.28 MeV	64 h
^{32}P	β	1.71 MeV	14.3 days
^{188}Re	β	2.12 MeV	17 h
^{186}Re	β	1.08 MeV	90.6 h
$^{188}W/Re$	β	2.12 MeV	69.4 days
^{133}Xe	β	0.35 MeV	5.25 days
^{131}I	β, γ	0.81 MeV (β) 723 keV (γ)	8.04 days
^{99m}Tc	γ	140 keV	6.02 days

Table 1.3
Isotopes used for intracoronary brachytherapy.

Ideally, the dose distribution should be given to the area injured by balloon angioplasty, while keeping the dose to the surrounding tissues as low as possible. Irradiation times should be less than 10 min to minimize the risk of acute thrombosis and other coronary complications during treatment. This would require either high-activity γ-sources (>100-mCi activity), introducing safety issues for both patient and personnel, or β-sources of 10–100 mCi. The radiation source should have dimensions, stiffness and flexibility compatible for use in complex coronary lesions. From a cost-effectiveness point of view, the used radioisotope, when using a catheter-based system, should have a sufficiently long half-life so that it may be used during several treatments over a long period of time.[39,40]

Not only the total radiation dose, but also the dose rate, is important, since damage caused by radiation can be repaired between fractionated doses or during low-dose-rate exposure. Therefore, the dose rate effect should be accounted for when comparing results of treatments using high dose rates with those of treatments using low dose rates. Cell death is markedly demonstrated in vitro at dose rates between 1 and 100 cGy/min.[49,50] Curiously, an in vitro experiment with human cells has shown that a dose rate of 0.6 cGy/min causes more cell death than 0.2 or 2.6 cGy/min. The explanation given for this inverse dose rate effect is that continuous irradiation at a dose rate of approximately 0.6 cGy/min effectively blocks cells in the mitosis (G_2) phase of the cell cycle, which is known to be more radiosensitive, thereby causing more cell death.[39]

Centering versus non-centering

A more homogeneous dose distribution is obtained by centering the radiation source with a balloon catheter (Figure 1.2). However, even with a centered source, eccentric intraluminal positioning (caused by, for example, an angulated lesion or a heavily calcified plaque) will result in areas of both relative underdose and overdose. Another example: if an artery has a curvature radius of 1 cm, the dose along the concave curvature of the artery will be 10–15% higher compared to the convex curvature, since the source will be closer to the concave curvature.[39,51] This could become clinically important,

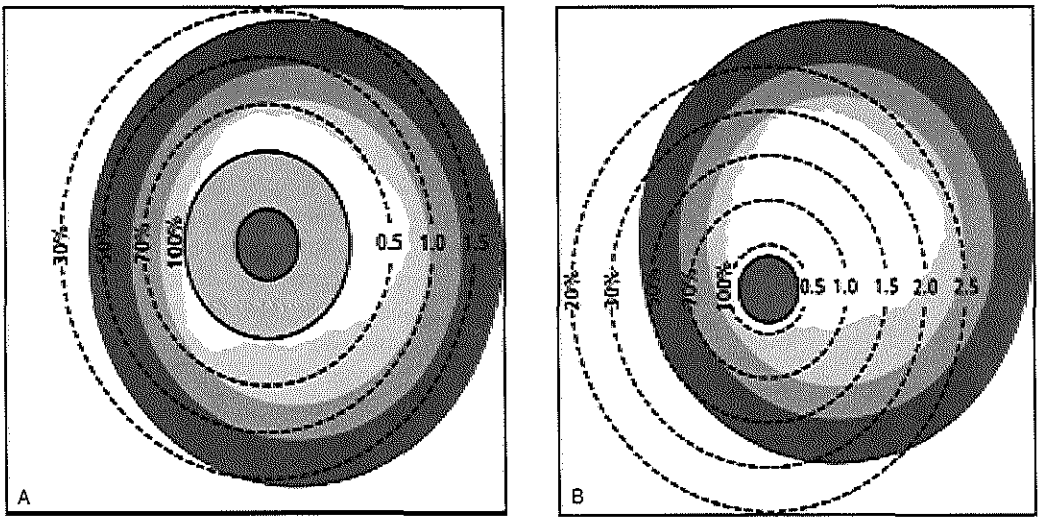


Figure 1.2
Dose distribution differences in centered versus non-centered sources. A centered source (A) delivers a more homogenous dose to the vessel wall compared to a non-centered source (B).

since low doses may stimulate neointimal proliferation,[32,52] and high doses can give rise to the development of aneurysms.[37]

γ-*Radiation versus* β-*radiation*

From a radiobiological point of view, it is unimportant whether γ-radiation, β-radiation or X-radiation is used. An equal dose, given to the same location at an equal dose rate, will lead to an equal biological effect.[53]

γ-Radiation has the following advantages. It deeply penetrates into the tissue, making it ideal for the treatment of large vessels (Figure 1.3). γ-Radiation is not shielded by stents, making it ideal for the treatment of in-stent restenosis. The most important advantage of γ-therapy is that it is the first treatment showing a reduction of restenosis in several large randomized, double-blind, placebo-controlled trials (Table 1.4). The disadvantages of γ-therapy are as follows: γ-Rays penetrate through normally used lead shields. A 1-inch lead shield is required to block the γ-rays. When high-energy γ-radiation is used, all 'unnecessary' personnel must leave the catheterization laboratory in order to limit their exposure to radiation. Overall, the patient and personnel receive higher radiation doses from a γ-radiation procedure in comparison to a β-radiation procedure. This problem of radiation exposure limits the maximal specific activity used for γ-therapy. Lower specific activities, however, result in longer dwell times (8–20 min) to achieve the same therapeutic doses, making total procedure times longer, which in turn increases the risk of cardiac events.[40,54]

The advantages of β-radiation are as follows: Thick plastic is able to shield β-energy. Since β-radiation only penetrates a few millimeters into the surrounding area, exposure to β-energy is limited. Therefore, higher specific activities can be used, making dwell times shorter (3–10 min) and total procedure times shorter. Additional radiation exposure to the patient and personnel

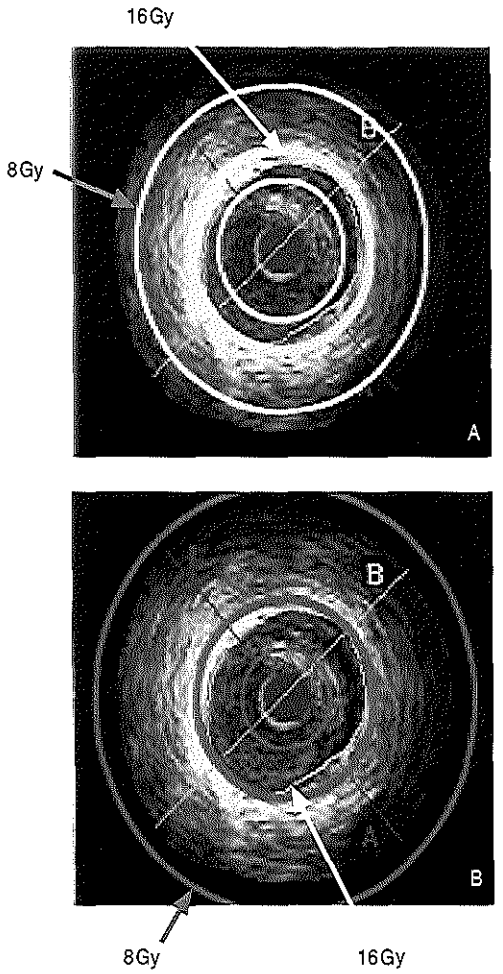


Figure 1.3
Example of the differences of isodose contours of β- and γ-radiation. With γ-radiation (B) the minimum effective dose of 8 Gy (gray arrow), inhibiting neointimal proliferation, extends further into the surrounding tissue, compared to β-radiation (A). Therefore, γ-radiation is preferable to β-radiation in large coronary vessels.

is negligible. Healthcare personnel can therefore remain in the catheterization laboratory. β-Therapy also has disadvantages. While results from clinical trials (Table 1.5) are encouraging, and its efficacy for in-stent restenosis has been recently reported[55] (JJ Popma ACC2000 presentation about the START trial), its efficacy for de novo or restenotic lesions remains to be proven by a randomized, double-blind, placebo-controlled trial. Owing to the steeper depth–dose fall-off curve, β-energy will probably not be able to treat vessels with diameters >4 mm and/or will require centering devices to ensure homogenicity of the dose (Figures 1.2 and 1.3). β-Energy has also been shown to be partially shielded by stents and calcified plaques, which may require an increase in the prescribed dose of up to 20%. Finally, dose distribution calculations of β-emitters are more complicated than those of γ-emitters.[40,54,56]

While working with β-radiation is obviously easier, γ-radiation has been used for several years without causing significant problems.[40,54]

Radioactive stents

One of the advantages of a β-particle-emitting radioactive stent is that the radioactive source is centered and in close contact with the vessel wall. Another advantage is the short procedure time, since the implantation time of a radioactive stent is equal to that of a non-radioactive stent. The dose distribution, however, will not be uniform, given the gridded structure of the stent and the concomitant inhomogeneous distribution of the radioactive source.[39] This might not be a problem if the concept of an electron-beam fence is true.[57] According to this concept, the radiation emitted by the stent generates a fence at the endoluminal surface, which prevents smooth muscle cells and myofibroblasts from migrating into the stent.[58]

The results of the clinical data so far are rather disappointing, with restenosis rates of up to 52% (Table 1.6).[59–61] While strict in-stent restenosis is observed to decrease with increasing levels of radiation doses, edge restenosis is the main cause of target lesion revascularization at high dose levels (Figure 1.4).[60,61] This edge restenosis is probably caused by a combination

Study	No. of patients	Gy	Lesion length (mm)	Source	Restenosis rate	MACE
SCRIPPS	53	8–30[a]	<30	^{192}Ir	17	15
				Placebo	54	48
WRIST	130	15[b]	<47	^{192}Ir	22	35
				Placebo	60	68
Long WRIST	120	15[b]	36–80	^{192}Ir	46	NA
				Placebo	78	NA
GAMMA-1	252	8–30[a]	<45	^{192}Ir	33	28
				Placebo	55	44
GAMMA-2	125	14[b]	<45	^{192}Ir	34	30

MACE, major cardiac events; NA, not available.
[a] To EEM. [b] Dose at 2 mm from the source.

Table 1.4
Results of placebo-controlled γ-radiation trials at 6-month follow-up.

Study	No. of patients	Gy	Lesion length (mm)	Source length (mm)	Source	Restenosis rate	MACE
Geneva	15	18[a]	<20	29	^{90}Y	40	33
BERT	20	12, 14, 16[b]	≤15	30	Sr/90Y	15	15
BERT 1.5	35	12, 14, 16[b]	<20	30	Sr/^{90}Y	11	9
Beta WRIST	50	20.6[c]	≤47	29	^{90}Y	34	34
					Placebo+	71	76
BRIE	149	14, 18[b]	<20	30	Sr/^{90}Y	34	34
Dose Finding Study	181	9, 12, 15, 18[c]	<15	29	^{90}Y 9 Gy	9	16
					^{90}Y 18 Gy	26	13
PREVENT	96	16, 20, 24[d]	<22	27	^{32}P	22	26
					Placebo	50	32
START	396	18, 20[b]	<20	30	Sr/^{90}Y	29	18
					Placebo	45	25.9
Compassionate use Rotterdam	18	16, 20[b]	<30	30	Sr/^{90}Y	53	47

MACE, major cardiac events.
[a] Dose at the inner arterial surface. [b] Dose at 2 mm from the source. [c] Dose at 1 mm from balloon. [d] Dose at 1 mm into vessel wall. + 50 placebo patients from WRIST.

Table 1.5
Results of β-radiation trials at 6-month follow-up.

Study	No. of patients	Stent activity (μCi)	Lesion length (mm)	Restenosis rate	TLR
IRIS 1A	32	0.5–1.0	<15	31	21
IRIS 1B	25	0.75–1.5	<15	50	32
IRIS Heidelberg	11	1.5–3.0	<15	54	NA
IRIS Rotterdam	26	0.75–1.5	<28	17	12
P32 Dose Response Rotterdam	40	6.0–12	<28	44	25
P32 Dose Response Milan	23	0.75–3.0	<28	52	52
	29	3.0–6.0		41	41
	30	6.0–12		50	50
	40	12–21		30	30

NA, not available; TLR, target lesion revascularization.

Table 1.6
Results of ^{32}P radioactive stents at 6-month follow-up.

of balloon trauma and low-dose radiation at the stent edge, so geographical miss occurs in all cases. Since geographical miss has been shown to be one of the determinants of edge restenosis,[62] future therapies will concentrate on the prevention of geographical miss by minimizing trauma and/or increasing radiation dose at the edges. Several new therapies are currently under investigation. Square-shouldered balloons, used for stent deployment, in which the entire balloon remains within the stent, will minimize barotrauma at the proximal and distal edges. Cold end stents, in which the center of the stent is made radioactive, while the proximal and distal 5 mm of the stent edges are non-radioactive, may decrease edge restenosis, if this restenosis is caused by negative remodeling. Another option is the implantation of hot end stents, in which the stent edges are made more radioactive compared to the center of the stent, thereby decreasing the chance of geographical miss.

Limitations of brachytherapy

Unfortunately, vascular brachytherapy has its limitations, which include the following:

- Low radiation doses (4–8 Gy) may stimulate neointimal proliferation.[52,63] This could be due to the fact that growth factors are synthesized de novo and secreted by surviving cells.[64] These growth factors promote the proliferation of smooth muscle cells.[65]
- Delayed depletion of some cells (adventitial cells, fibroblasts) could lead to subsequent repopulation, whereby smooth muscle cells from the media could be progressively replaced by fibroblasts and extracellular matrix, leading to fibrosis, as has been previously described in animal experiments.[22,29]
- Persisting dissections after β-radiation have been observed at 6-month angiographical follow-up[66,67] (Figure 1.5).
- Geographical miss, where the injured area is not completely covered by the irradiated area, is a major cause of edge restenosis (Figure 1.6). The incidence of geographical miss ranges from 18% to 34%. In case of geographical miss, a restenosis rate of 39% was seen, versus 9% when there was no geographical miss.[68] Geographical miss increases the chance of restenosis up to four fold. Edge restenosis has been observed at the edges of

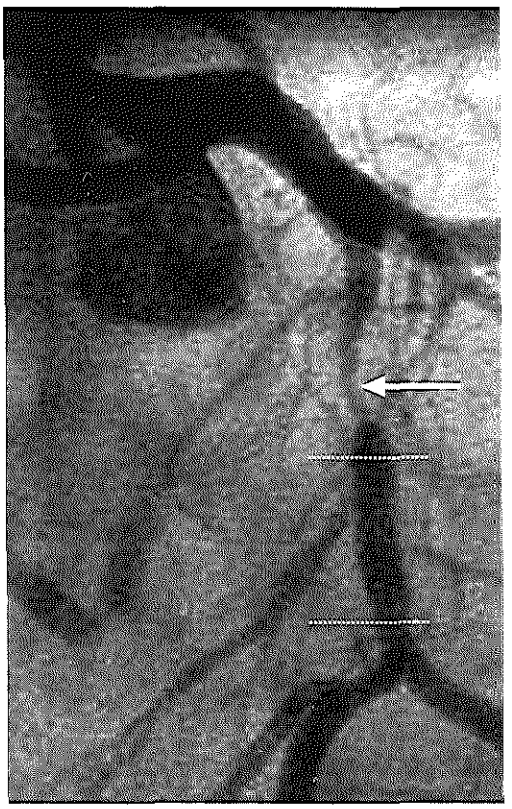


Figure 1.4
Example of edge restenosis. At 6-month angiographic follow-up, a radioactive stent (proximal and distal ends marked by the dotted lines) shows an excellent result. However, at the proximal edge, a severe edge restenosis (white arrow) is observed.

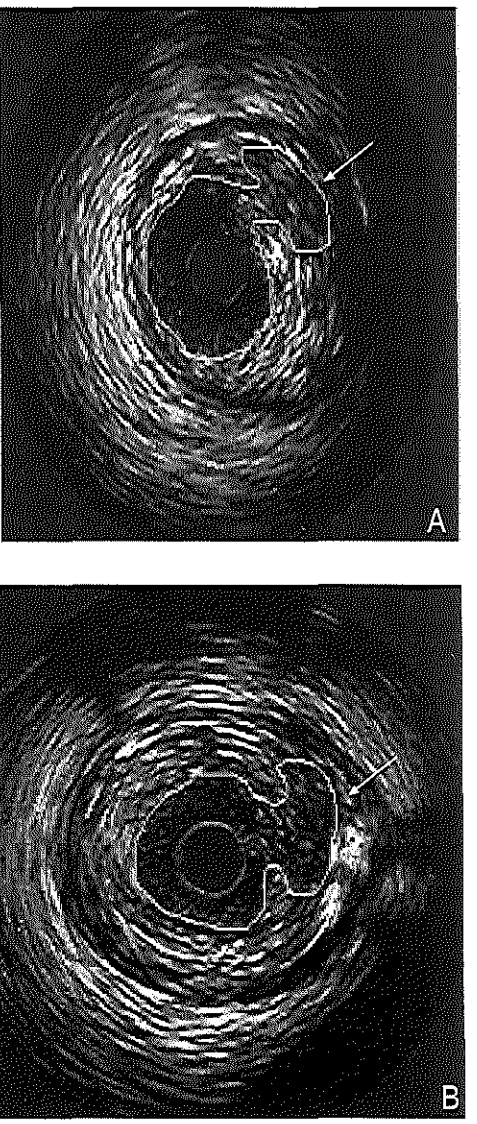


Figure 1.5
Example of a persisting dissection.
(A) Post-procedure, a dissection (white arrow) is observed by intravascular ultrasound.
(B) At 2-year follow-up, the dissection (white arrow) remains unhealed.

the treated area. It appears to occur when the area injured by the balloon is larger than the irradiated area[69] (Figure 1.7).

- Mid-term (2–3-year) follow-up indicates signs of delayed rather than inhibited restenosis[70–72] (Figures 1.8 and 1.9)
- Black holes are observed in 22–39% of cases at 6-month intravascular ultrasound (IVUS) follow-up of the cases at the Thoraxcenter. They are called black holes because they are

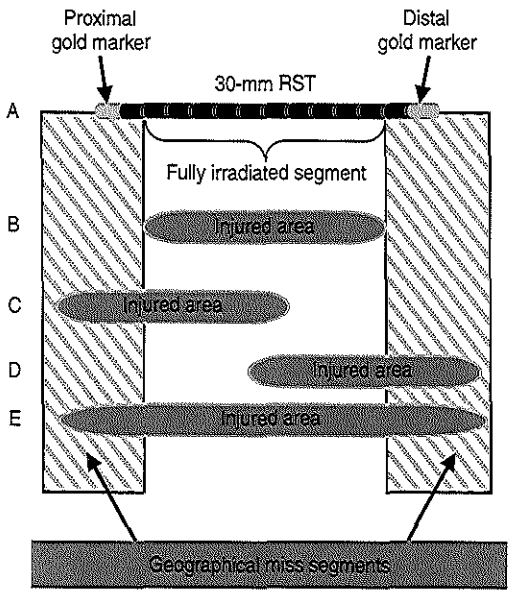


Figure 1.6
Explanation of geographical miss.
(A) A radiation source train (RST) of 30-mm length. Because of the dose fall-off at both ends, the fully irradiated segment is smaller than the total length of the source train.
(B) No geographical miss: the injured area is fully covered by the RST.
(C) Proximal geographical miss: the injured area is proximal not covered by the RST.
(D) Distal geographical miss: the injured area is distal not covered by the RST.
(E) Proximal and distal geographical miss: the injured area is both proximal and distal not covered by the RST.

echolucent on IVUS. Pathology reveals smooth muscle cells in the extracellular matrix containing abundant proteoglycans and an absence of elastin and mature collagen. Sixty percent of the black hole cases have angiographic restenosis.

Whether these limitations will reduce the use of brachytherapy remains unknown.

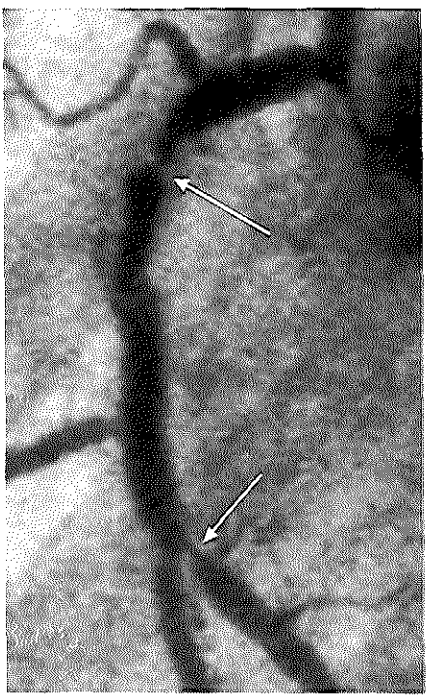
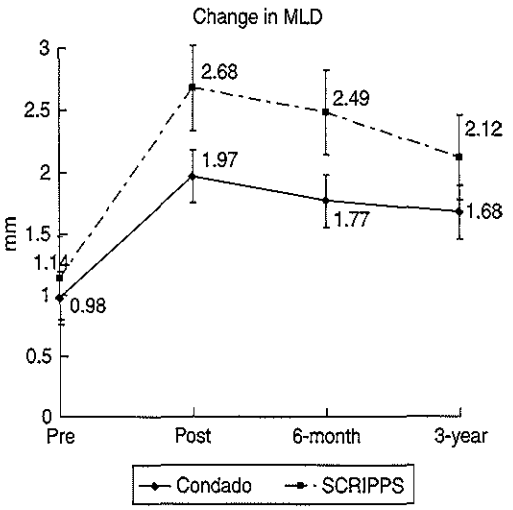


Figure 1.7
Example of proximal and distal geographical miss, resulting in a candy wrapper edge restenosis (white arrows) at 6-month follow-up.

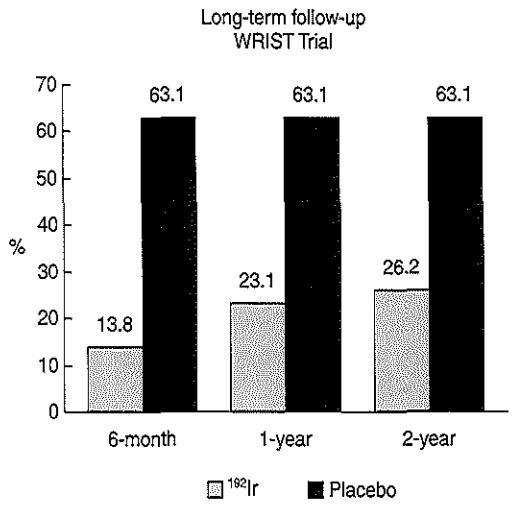
Safety issues of brachytherapy

Work with radiation therapy must be performed with extreme care, because of the following safety issues:

- The risk of perforation will probably be small, especially when keeping the dose delivered to the adventitia low.[30]
- Aneurysm formation (Figure 1.10) seems to be dose related and has been observed in patients receiving high radiation doses of up to 92 Gy.[37] However, in other trials,[30,46,73–75] using lower doses of up to 30 Gy, no excessive aneurysm formation has been observed.
- A dose-dependent delay in endothelialization of the stent has been shown, which might increase the chance of subacute thrombo-

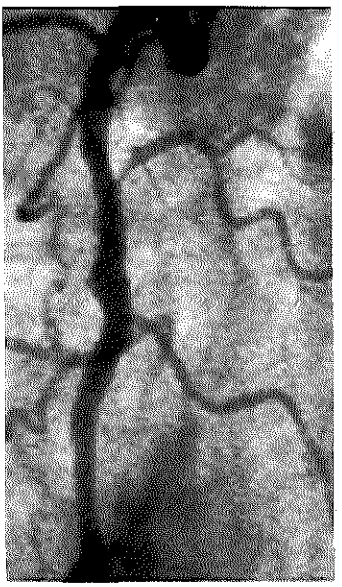


A

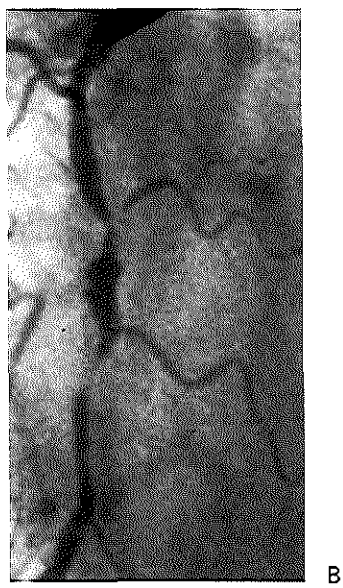


B

Figure 1.8
Indications of delayed, rather than inhibited, restenosis after intracoronary brachytherapy.
(A) Both the Condado and the SCRIPPS trial show a continuing loss of MLD, after 6-month follow-up.
(B) During 2-year follow-up, the restenosis rate remains stable at 65.1% in the placebo group, while it increases from 13.8% to 26.2% in the irradiated group.



A



B

Figure 1.9
Example of delayed restenosis.
(A) Good angiographic result, 6 months after intracoronary brachytherapy.
(B) In the same patient, 16 months after treatment, a severe candy wrapper edge restenosis is observed.

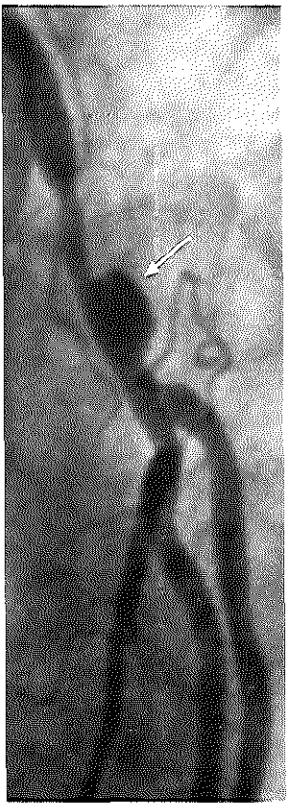


Figure 1.10
Example of a coronary aneurysm (white arrow), 6 months after intracoronary brachytherapy.

sis.[29,76] Also, in patients treated by catheter-based brachytherapy, with and without stent implantation, late thrombotic occlusions, with an incidence of up to 11%, have been observed.[77] Therefore, all patients treated with coronary brachytherapy should receive either ticlopidine or clopidogrel for at least 6 months and aspirin indefinitely.

- Vessel enlargement (positive remodeling) due to brachytherapy can induce late stent malapposition, which may result in late stent thrombosis,[78] which is another reason for prolonged, or even lifelong, antiplatelet therapy.
- High doses of radiation (>35 Gy) applied to larger tissue areas, used for the treatment of neoplasms, result in accelerated coronary artery disease.[79–81] Intermediate doses (30–40 Gy) have shown a low risk of cardiac disease during long-term follow-up (mean 11 years).[82]
- Radiation-induced carcinogenesis is of great concern; however, since irradiation delivers an extremely low dose beyond the immediate lesion, and the exposed tissues (e.g. arteries, veins, cardiac muscle, and pericardium) have a low spontaneous carcinogenicity rate, this risk appears to be extremely low.[30,75]

The safety of radiation therapy for benign diseases has been confirmed for periods of more than 20 years.[26] Also, the safety of peripheral vascular brachytherapy during a 6-year follow-up has been reported.[46] Recently, the 2-year follow-up of patients treated with intracoronary brachytherapy has shown no signs of late clinical effects.[30]

Indications

Intracoronary brachytherapy should be given to patients at high risk of developing restenosis. Therefore, brachytherapy should be given to patients with:

- in-stent restenosis
- long lesions
- multivessel disease
- saphenous vein graft lesions
- small coronary artery lesions
- diabetic disease
- renal insufficiency.

Contraindications

Intracoronary brachytherapy should not be given if the patient has a high risk of receiving a too-high cumulative dose at the vessel wall. This is

possible in patients with:

- previous radiotherapy of the chest
- previous intracoronary brachytherapy, in case of previous γ-irradiation, or previous brachytherapy of the treated vessel segment, in case of previous β-irradiation.

Conclusion

Intracoronary brachytherapy is a promising new therapy for the treatment of in-stent restenosis. Whether it may also prevent restenosis after balloon angioplasty for de novo or restenotic lesions will be known by the end of the year 2000, when the 6-month angiographical follow-up data of current ongoing trials will be available. Long-term clinical and angiographical follow-up is also necessary, to ensure long-term safety and efficacy.

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Part 2

Dose Finding Studies.

Chapter 3

β-Particle-emitting radioactive stent implantation. A safety and feasibility study.

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β-Particle–Emitting Radioactive Stent Implantation

A Safety and Feasibility Study

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Background—This study represents the Heart Center Rotterdam's contribution to the Isostents for Restenosis Intervention Study, a nonrandomized multicenter trial evaluating the safety and feasibility of the radioactive Isostent in patients with single coronary artery disease. Restenosis after stent implantation is primarily caused by neointimal hyperplasia. In animal studies, β-particle–emitting radioactive stents decrease neointimal hyperplasia by inhibiting smooth muscle cell proliferation.

Methods and Results—The radioisotope ^{32}P, a β-particle emitter with a half-life of 14.3 days, was directly embedded into the Isostent. The calculated range of radioactivity was 0.75 to 1.5 μCi. Quantitative coronary angiography measurements were performed before and after the procedure and at 6-month follow-up. A total of 31 radioactive stents were used in 26 patients; 30 (97%) were successfully implanted, and 1 was embolized. Treated lesions were in the left anterior descending coronary artery (n=12), the right coronary artery (n=8), or the left circumflex coronary artery (n=6). Five patients received additional, nonradioactive stents. Treated lesion lengths were 13±4 mm, with a reference diameter of 2.93±0.47 mm. Minimum lumen diameter increased from 0.87±0.28 mm preprocedure to 2.84±0.35 mm postprocedure. No in-hospital adverse cardiac events occurred. All patients received aspirin indefinitely and ticlopidine for 4 weeks. Twenty-three patients (88%) returned for 6-month angiographic follow-up; 17% of them had in-stent restenosis, and 13% had repeat revascularization. No restenosis was observed at the stent edges. Minimum lumen diameter at follow-up averaged 1.85±0.69 mm, which resulted in a late loss of 0.99±0.59 mm and a late loss index of 0.53±0.35. No other major cardiac events occurred during the 6-month follow-up.

Conclusions—The use of radioactive stents with an activity of 0.75 to 1.5 μCi is safe and feasible. (***Circulation.* 1999;100:1684-1689.**)

Key Words: β-rays ■ angioplasty ■ radioactive isotopes ■ restenosis ■ stents

Percutaneous transluminal coronary angioplasty (PTCA) is an accepted treatment for coronary artery disease.[1] However, angiographic restenosis is reported in 40% to 60% of patients after a successful PTCA.[1,2] The main mechanisms of restenosis include late constriction of the arterial wall (vascular shrinkage) and neointimal hyperplasia,[3–6] which are due to the migration and proliferation of smooth muscle cells and myofibroblasts after balloon-induced trauma of the arterial wall and the deposition of an extracellular matrix by the smooth muscle cells.[6–9] Stent implantation reduces the restenosis rate[10,11] by preventing elastic recoil and late constrictive remodeling.[12] However, the occurrence of restenosis after stent implantation remains unresolved, especially in small vessels and long lesions, in which it may occur in >30% of cases.[13] Restenosis is primarily caused by neointimal hyperplasia, which occurs due to trauma of the arterial wall by the stent struts.[5]

Irradiation is used to decrease neointimal proliferation because the actively proliferating cells have an increased sensitivity to the lethal effects of radiation, which inhibits benign hyperplastic reactions such as keloid formation and heterotopic ossification.[14,15] Several experimental and clinical trials showed that brachytherapy with a radioactive source after PTCA or stent implantation can reduce restenosis by inhibiting neointimal hyperplasia,[16–19] and several animal studies demonstrated a dose-related reduction of in-stent restenosis with the use of radioactive stents.[20–22] Furthermore, a dose-dependent delay in the endothelialization of the stent occurred, which increased the chance of subacute thrombosis.[20,23]

This study evaluated the safety and feasibility of radioactive stent implantation (activity level, 0.75 to 1.5 μCi) in single-lesion, native coronary artery disease.

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TABLE 1. Balloon Inflation and Stent Deployment Data

Patient	Type of Stent	Predilatation			Stent Deployment		Postdilatation			Lesion Length, mm
		Diam, mm	Atm	Length, mm	Diam, mm	Atm	Diam, mm	Atm	Length, mm	
1	PS‡	3.0	6	20	3.0	10	3.5	16	30	17
2	PS	3.0	8	20	3.5	8	3.0	16	15	11
3	PS	3.5	14	30	3.5	10	3.5	16	13	10
4	PS	3.5	8	30	3.5	12	ND	ND	ND	15
5	BX*	2.5	14	20	3.0	12	3.5	16	13	15
6	BX	3.5	6	20	3.5	10	4.0	12	13	12
7	PS	3.0	10	20	3.0	12	3.5	10	13	11
8	BX	4.0	6	15	3.5	12	4.5	16	15	10
9	BX	2.5	6	15	3.5	16	2.5	12	15	14
10	BX	3.5	10	20	3.5	11	4.0	18	13	19
11	BX*	3.0	12	13	3.5	11	4.0	18	13	8
12	BX†*	3.0	10	20	3.0	12	3.0	18	20	17
13	BX*	3.0	10	20	3.0	8	3.5	16	13	17
14	BX	3.0	8	15	3.5	12	ND	ND	ND	14
15	BX	3.0	12	13	3.0	10	4.0	14	13	7
16	BX	3.0	12	13	3.0	10	4.0	16	13	10
17	BX	3.5	12	20	3.5	8	4.0	16	13	12
18	BX†	3.0	8	20	3.0	10	4.0	18	20	23
19	BX	3.5	7	20	3.5	7	4.0	14	13	10
20	BX†	3.0	14	29	3.0	18	3.5	16	29	15
21	BX	3.5	8	20	3.5	8	ND	ND	ND	12
22	BX	3.5	8	15	3.5	8	4.0	12	13	10
23	BX†	3.0	10	20	3.5	10	4.0	16	20	16
Mean		3.2	10	19	3.3	11	3.7	15	16	13
SD		0.4	3	5	0.2	3	0.5	2	5	4

Atm indicates maximum atmospheres; Diam, maximum diameter; ND, not done; PS, Palmaz-Schatz.
*1 additional nonradioactive stent implanted; †2 BX stents implanted; ‡2 additional nonradioactive stents implanted.

Methods

Patient Population

The Isostents for Restenosis Intervention Study (IRIS) is a nonrandomized, multicenter trial evaluating the safety and feasibility of radioactive stents. The data presented here represent the experience of the Heart Center Rotterdam. Patients who had single coronary lesions with a maximum lesion length of 28 mm (maximum, 2 radioactive stents of 15 mm implanted in tandem position) and objective evidence of ischemia were eligible. Exclusion criteria included the following: a recent myocardial infarction (MI: creatine kinase [CK] isoenzyme containing M and B subunits [MB] >3 times the upper limit of normal within 5 days of the intervention); left ventricular ejection fraction <40%; allergy or contraindication to aspirin, ticlopidine, or stainless steel; and lesions located in the left main artery or at the ostium of the right coronary artery. The Medical Ethical Committee of the University Hospital Rotterdam approved the study. All patients provided written, informed consent before the procedure.

Radioactive Stent, Dosimetry, and Safety Issues

Two types of stents were implanted in this study: the Palmaz-Schatz (Cordis Corp, Johnson and Johnson Interventional Systems Co) and BX stent (Isostent Inc). Phosphorus-32 (^{32}P), a pure β-emitter with a half-life of 14.3 days, was produced by neutron irradiation of red amorphous ^{31}P for 10 days to achieve a concentration of 20×10^{-6} $^{32}P/^{31}P$ (100 mCi). The irradiated phosphorus was then placed into a mass separator, ionized, and accelerated. A dipole magnet separated the ^{32}P and ^{31}P. Subsequently, ^{32}P was directly implanted into the metal stent surface.[21] The calculated radioactivity of the stents at implantation was 0.75 to 1.5 μCi, and the dose delivered over 100 days at 1 mm from the stent surface was calculated for each stent. All personnel were trained in the appropriate handling of radioactive materials. During implantation, the lucite shield enclosing the stent and the sheathed introduction system prevented exposure of the operator to the radiation of the stent. Background measurements of radioactivity were made by means of a Geiger counter (Model 14c, Ludlum Measurements Inc). All disposable materials that were in contact with the stent were immediately disposed of in a plexiglas container, and radioactivity measurements were made by the radiation technician.

Quantitative Coronary Angiography

Quantitative coronary angiography (QCA) was performed preprocedure, postprocedure, and at 6-month follow-up. Coronary angiography was performed after intracoronary administration of nitrates. The off-line analysis of ≥2 orthogonal projections was performed by the CAAS II analysis system (Pie Medical BV). Calibration of the system was based on dimensions of the catheters not filled with contrast medium. This method of analysis has been extensively validated and applied in numerous clinical trials.[24–26] The following measurements were obtained in each projection: minimum lumen diameter (MLD), reference diameter, percent diameter stenosis (%DS), and lesion length. Lesion length was user-defined.[26] Procedural success was defined as <20% DS as measured by online QCA. The acute gain was defined as MLD postprocedure minus MLD

preprocedure. Late loss was defined as MLD postprocedure minus MLD at follow-up. Late loss index was defined as late loss divided by acute gain.[27] Restenosis was defined as >50% DS at follow-up located within the stent or ≤5 mm from the stent edges. The latter represents an area where tissue is subjected both to balloon-induced trauma and to a lower dose of radiation,[21] which may stimulate restenosis. This edge-effect phenomenon has recently been described in patients and called the "candy-wrapper effect."[28] To quantify an edge effect, a QCA segmental analysis was performed. At both postprocedure and follow-up, the treated vessels were first divided into segments ≈5 mm in length; then, the mean diameter of the 5-mm segments distal and proximal to the stent edges were calculated using the CAAS II analysis system. Careful comparison of the proximal and distal edges was performed postprocedure and at follow-up.

Procedure and Follow-Up

Patients received 250 mg of aspirin and 10 000 IU of heparin at the start of the procedure. The activation clotting time was maintained at >300 s. After balloon predilatation, the radioactive stent was implanted at a nominal deployment pressure of 8 to 10 atm. If needed, stent deployment was optimized using shorter postdilatation balloons of longer diameters to higher pressures (Table 1). Extreme care was taken to avoid inflating the balloon outside the edges of the stent. Because of the poor radiopacity of the Palmaz-Schatz and the BX stents, the best angiographic view was selected, and images were filmed in a magnified field (5 inch) with digital zoom enhancement to optimize stent visualization. All patients received ticlopidine 250 mg BID for 4 weeks after stent implantation and aspirin 80 mg daily indefinitely. CK and CK-MB measurements were made, and the ECG was recorded at 6 and 12 to 18 hours postprocedure in all patients.

Patients returned for 1- and 6-month clinical follow-up. An ECG was performed at each visit. The 30-day and 6-month clinical end points were death, Q-wave MI (using the Minnesota code criteria[29]), non Q-wave MI (CK-MB rise >2 times normal upper limit), bypass surgery, target segment revascularization, sustained abrupt closure, or subacute thrombosis of the target vessel.

At the 6-month visit, an exercise stress test was performed. Target vessel revascularization was performed on the basis of clinical symptoms and/or evidence of ischemia on exercise testing.

Statistical Analysis

Data are presented as mean±SD. Continuous data were compared by 2-tailed Student's *t* test or linear regression when appropriate.

Results

Baseline Characteristics

Baseline demographics, anginal status, and lesion characteristics are shown in Table 2.

Procedural Success

A total of 30 of the 31 stents (97%) were successfully implanted (26 were BX Isostent and 4 were Palmaz-Schatz) in 26 patients. One stent (BX) was lost in the peripheral circulation without clinical sequelae. Eighteen patients were successfully treated with a single radioactive stent, and 4 required a second radioactive stent to cover lesions >15 mm. Five patients received additional nonradioactive stents: 2 due to procedural dissection not covered by the radioactive stent, 2 because a second radioactive stent was not available, and 1 because a second radioactive stent became dislodged when trying to implant it distal to the first radioactive stent. All procedures were successful, and no complications occurred.

TABLE 2. Patient Demographics

Sex, male/female	18/8 (69/31%)
Age, y	
Average	60
Range	43–74
Risk factors	
Diabetes mellitus	1 (4%)
Hypercholesterolaemia	16 (62%)
Hypertension	11 (42%)
Smoking	15 (58%)
Family history	11 (42%)
AP CCS	
2	3 (12%)
3	10 (38%)
4	13 (50%)
Lesion type, AHA/ACC	
B1	8 (31%)
B2	18 (69%)

Data are n (%) unless otherwise indicated. AHA indicates American Heart Association, and ACC, American College of Cardiology.

Follow-Up

The mean hospital stay was 1.8 days. All patients were angina-free at hospital discharge. At 30-day follow-up, no clinical end points had occurred: 24 patients (92%) were asymptomatic, and 2 patients (8%) had recurrent angina pectoris (AP) of Canadian Cardiovascular Society Classification (CCS) 1 (n=1) and CCS 2 (n=1). All 26 patients returned for 6-month clinical follow-up. Twenty-one (81%) were asymptomatic, and 5 patients (19%) had AP CCS 1 (n=1), CCS 2 (n=2), CCS 3 (n=1), or CCS 4 (n=1).

Six-month angiographic follow-up was performed in 23 patients (88%). The remaining 3 patients (12%) refused: 2 of them were asymptomatic, and the third had AP CCS 1. Four patients had angiographic restenosis (17%). All restenotic lesions were diffuse (located throughout the entire length of the stent). One of the 4 restenoses occurred in a patient with a single radioactive stent, 1 restenosis was in a patient receiving 2 radioactive stents in combination with a nonradioactive stent, and 2 restenoses were observed in patients receiving a combination of 1 radioactive and 1 nonradioactive stent. In the restenotic patients who received an additional nonradioactive stent, restenosis occurred in both the radioactive and the nonradioactive stent. On QCA, no discernible differences existed between the patterns of proliferation between the Palmaz-Schatz and BX stents. No cases of restenosis at the stent edges were noted. Two of the 4 restenotic patients underwent a re-PTCA. One was referred for bypass surgery for in-stent restenosis in the proximal left anterior descending coronary artery and progression of a previously nonsignificant lesion in the proximal left circumflex artery (main stem equivalent). One was treated medically; this patient was asymptomatic, with a negative stress test. No other clinical end points existed at 6-month follow-up.

TABLE 3. Dosimetry and QCA Analyses

Patient	Type of Stent	Activity, μCi	Dose, cGy	Artery	Lesion Length, mm	Preintervention			Postintervention			Follow-Up			Acute Gain	Late Loss	LLI
						MLD	DS	RD	MLD	DS	RD	MLD	DS	RD			
1	PS‡	1.07	712	RCA	17	0.65	76	2.64	2.48	19	3.04	1.74	30	2.51	1.83	0.74	0.40
2	PS	1.07	712	LAD	11	1.02	52	2.12	2.56	8	2.78	0.54	77	2.39	1.54	2.02	1.31
3	PS	0.97	647	LCX	10	0.46	85	3.05	2.93	15	3.41	2.77	18	3.36	2.47	0.16	0.06
4	PS	0.97	647	RCA	15	0.75	79	3.50	2.91	22	3.73	1.60	47	3.01	2.16	1.31	0.61
5	BX*	1.07	712	LAD	15	0.90	59	2.22	2.80	9	3.07	0.47	87	3.61	1.90	2.33	1.23
6	BX	1.50	1000	RCA	12	1.64	53	3.49	3.06	15	3.59	2.45	23	3.18	1.42	0.61	0.43
7	PS	0.75	500	LAD	11	0.67	75	2.67	2.64	15	3.12	1.58	39	2.58	1.97	1.07	0.54
8	BX	1.24	824	RCX	10	0.99	74	3.65	3.51	19	4.31	2.76	44	4.20	2.52	0.75	0.30
9	BX	1.12	748	RCX	14	0.50	77	2.08	1.92	12	2.19	1.77	26	2.39	1.43	0.16	0.11
10	BX	1.73	1157	LAD	19	0.99	71	3.31	3.18	18	3.87	2.39	16	2.82	2.19	0.79	0.36
11	BX*	0.88	587	LAD	8	0.59	79	2.73	3.42	17	4.11	2.65	20	3.32	2.83	0.77	0.27
12	BX†*	1.24	827	LAD	17	1.00	58	2.37	2.36	16	2.81	0.86	55	1.90	1.37	1.51	1.10
13	BX*	1.36	908	LAD	17	0.69	72	2.45	2.48	14	2.87	1.73	11	1.94	1.80	0.76	0.42
14	BX	1.12	748	LAD	14	0.62	79	2.96	2.75	12	3.12	1.61	44	2.86	2.13	1.15	0.54
15	BX	1.02	678	RCX	7	0.49	83	2.81	3.03	16	3.59	2.20	25	2.91	2.54	0.83	0.33
16	BX	1.06	712	LAD	10	1.10	67	3.36	3.27	10	3.63	1.87	34	2.81	2.17	1.41	0.65
17	BX	1.43	953	RCA	12	0.85	75	3.44	2.92	9	3.19	0.83	70	3.29	2.07	2.09	1.01
18	BX†	1.00	678	RCA	23	0.83	73	3.08	2.99	5	3.07	2.51	28	3.47	2.15	0.48	0.22
19	BX	1.02	677	RCX	10	0.96	71	3.28	2.90	17	3.50	2.87	17	3.46	1.94	0.03	0.02
20	BX†	0.75	500	LAD	15	1.13	60	2.81	2.81	17	2.81	1.97	39	3.23	1.69	0.84	0.50
21	BX	1.43	953	RCX	12	1.23	62	3.31	2.89	21	3.61	2.03	39	3.34	1.66	0.85	0.51
22	BX	1.06	700	RCA	10	1.16	66	3.37	2.91	9	3.18	1.72	45	3.12	1.75	1.20	0.68
23	BX†	0.75	500	RCA	16	0.90	68	2.75	2.66	23	3.45	1.73	42	2.99	1.76	0.93	0.53
Mean		1.10	743		13	0.87	70	2.93	2.84	15	3.31	1.85	38	2.99	1.97	0.99	0.53
SD		0.25	165		4	0.28	9	0.47	0.35	5	0.48	0.69	20	0.54	0.39	0.59	0.35

Dose indicates dose over 100 days at 1 mm from the stent surface; DS, percentage diameter stenoses; LAD, left anterior descending artery; LCX, left circumflex artery; LLI, late loss index; PS, Palmaz-Schatz stent; RCA, right coronary artery; and RD, reference diameter. QCA measurements are in mm.

*1 additional nonradioactive stent implanted; †2 BX stents implanted; ‡2 additional nonradioactive stents implanted.

QCA Measurements

QCA and procedural data are presented in Table 3. MLD increased from 0.87±0.28 mm preprocedure to 2.84±0.35 mm postprocedure ($P<0.0001$). MLD at follow-up was 1.85±0.69 mm ($P<0.0001$ relative to postprocedure), resulting in a late loss index of 0.53±0.35. Segmental analysis of the mean diameter of the 5-mm segments distal and proximal to the stent edges showed significant changes. The proximal diameter decreased from 3.19±0.42 mm postprocedure to 2.78±0.62 mm at follow-up ($P=0.006$). The distal diameter decreased from 2.69±0.49 mm postprocedure to 2.45±0.50 mm at follow-up ($P=0.0167$).

Radiation Doses

Stent activity level and the cumulative dose over 100 days that was delivered to a 1 mm depth outside the stent are presented in Table 3. No correlation existed between stent activity or delivered dose and MLD or late loss index at follow-up. No additional environmental radiation was measured during the procedure.

Discussion

This nonrandomized study illustrates that β-particle–emitting radioactive stent implantation is safe and feasible, with no subacute or 30-day clinical events recorded. Subacute thrombosis was not seen, despite the concern regarding delay in endothelialization, as previously reported in animal studies.[20,23] The embolization of the radioactive stent had no clinical sequelae at this level of activity. When stents with higher levels of radioactivity are implanted, this may not remain true. Detecting an embolized radioactive stent is a problem because (1) the β-radiation of the stent is not measurable outside the body and (2) the stents have a relatively low radiopacity. Clearly, there is room to increase the radiopacity or to add markers to the stents.

Using a multivariate model constructed from the data of the Benestent trials that was based on similar lesions, vessel size, and short-term result, a predicted restenosis rate of 12% and an MLD at follow-up of 2.05 mm was calculated.[30,31] Thus, the actual results achieved are somewhat less favorable; however, in such a small patient cohort, no definite conclusions can be drawn except that the late results are within the

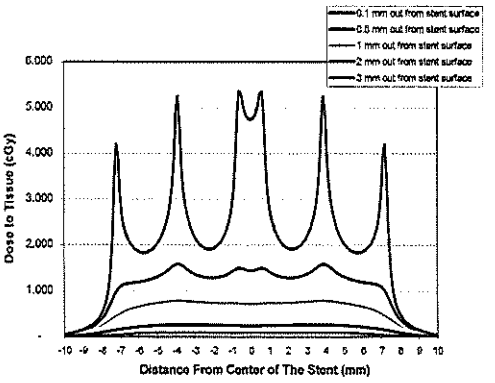

Figure 1. Two-dimensional dose representation for 1-μCi ^{32}P Palmaz-Schatz stent. Cumulative dose given over 100 days is shown (source, Isostent Inc).

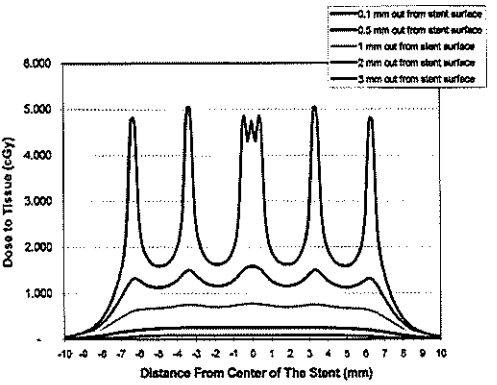

Figure 2. Two-dimensional dose representation for 1-μCi ^{32}P BX stent. Cumulative dose given over 100 days is shown (source, Isostent Inc).

acceptable limits for safety and feasibility of this stent. It must be noted that 3 of the 4 patients who had in-stent restenosis had multiple stents implanted, which increases the risk of restenosis; in the group of 18 patients who had a single radioactive stent implanted, only 1 had restenosis. Overall, these 6-month clinical and angiographic results are similar to the published results of nonradioactive stents.[10,11]

The Milan group was the first to report restenosis within the stent and at the edges of the stent (the candy-wrapper phenomenon); this restenosis was possibly caused by increased balloon injury (barotrauma) and the lower radiation dose at the stent edges.[21,28] In the Rotterdam series, particular attention was paid to avoiding balloon injury outside the stent to minimize the edge effect. No cases of edge restenosis were seen in this cohort; however, the proximal and distal mean diameter at the stent edges, measured postprocedure and at follow-up, decreased significantly. Because extreme care was taken to avoid inflating the balloon outside the stent edges, this edge effect may be caused by the lower radiation dose.

Dosimetry

Previous work by Janicki et al[32] on the 1.0-μCi Palmaz-Schatz stent demonstrated the nonuniformity of dosing in areas adjacent to stent strut wires and those areas between the wires. Models showed that for a ^{32}P stent of 1.0 μCi that was 15 mm in length, at a distance of 0.1 mm, dose values of 2500 cGy were delivered at the strut wires (peaks) and 800 cGy between the wires (valleys) over 1 half-life (14.3 days). The nonuniformity of dosing, reflective of stent geometry, decreased at distances 1 to 2 mm from the stent surface. Although these data provide an in-vitro analysis of dosing from a radioactive stent, the actual dose distribution is probably affected by variations in atherosclerotic plaque morphology and the symmetry of the lesion and stent expansion. The 2D dosimetry representation of the Palmaz-Schatz and BX stent were done using the Janicki model[32] (Figures 1 and 2).

Currently, dose-finding studies examining restenosis after implantation of ^{32}P BX stents in patients with lesion morphology similar to that described in this study are underway. It is possible that increased doses will decrease in-stent restenosis, as has been described in animal studies.[21–23] Therefore, a European Dose Response trial has been started with activities ranging from 1.5 to 3, 3 to 6, 6 to 12, and 12 to 20 μCi.

Conclusion

This study reports that the implantation of β-particle–emitting radioactive stents with an activity of 0.75 to 1.5 μCi is safe and feasible.

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Chapter 4

Clinical and angiographical follow-up after implantation of a 6.0-12.0 μCi radioactive stent in patients with coronary artery disease.

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Clinical and angiographical follow-up after implantation of a 6–12 μCi radioactive stent in patients with coronary artery disease

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Aims This study is the contribution by the Thoraxcenter, Rotterdam, to the European ^{32}P Dose Response Trial, a non-randomized multicentre trial to evaluate the safety and efficacy of the radioactive Isostent® in patients with single coronary artery disease.

Methods and Results The radioactivity of the stent at implantation was 6–12 μCi. All patients received aspirin indefinitely and either ticlopidine or clopidogrel for 3 months. Quantitative coronary angiography measurements of both the stent area and the target lesion (stent area and up to 5 mm proximal and distal to the stent edges) were performed pre- and post-procedure and at the 5-month follow-up. Forty-two radioactive stents were implanted in 40 patients. Treated vessels were the left anterior descending coronary artery (n=20), right coronary artery (n=10) or left circumflex artery (n=10). Eight patients received additional non-radioactive stents. Lesion length measured 10 ± 3 mm with a reference diameter of 3·07 ± 0·69 mm. Minimal lumen diameter increased from 0·98 ± 0·53 mm pre-procedure to 2·29 ± 0·52 mm (target lesion) and 2·57 ± 0·44 mm (stent area) post-procedure. There was one procedural non-Q wave myocardial infarction, due to transient thrombotic closure. Thirty-six patients returned for angiographical follow-up. Two patients had a total occlusion proximal to the radioactive stent. Of the patent vessels, none had in-stent restenosis. Edge restenosis was observed in 44%, occurring predominantly at the proximal edge. Target lesion revascularization was performed in 10 patients and target vessel revascularization in one patient. No additional clinical end-points occurred during follow-up. The minimal lumen diameter at follow-up averaged 1·66 ± 0·71 mm (target lesion) and 2·12 ± 0·72 (stent area); therefore late loss was 0·63 ± 0·69 (target lesion) and 0·46 ± 0·76 (stent area), resulting in a late loss index of 0·65 ± 1·15 (target lesion) and 0·30 ± 0·53 (stent area).

Conclusion These results indicate that the use of radioactive stents is safe and feasible, however, the high incidence of edge restenosis makes this technique currently clinically non-applicable.

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Key Words: β-particles, angioplasty, radioisotope, restenosis, stent.

See page 669 for the Editorial comment on this article

Introduction

In-stent restenosis is almost exclusively caused by neointimal hyperplasia formation, which occurs due to trauma of the arterial wall, caused primarily by the stent struts and balloon dilatations[1,2].

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Vascular brachytherapy with a radioactive source after PTCA or stent implantation has been shown, in several experimental and clinical trials, to be a promising treatment in reducing restenosis rates, by inhibiting the process of neointimal hyperplasia[3–6]. Several animal trials have demonstrated a dose-related reduction of in-stent restenosis, following radioactive stent implantation[7–9]. However, a dose-dependent delay in endothelialization of the stent has been shown, which increases the risk of subacute and late thrombotic occlusions[8,10]. Recently, a porcine coronary model indicated that continuous low-dose rate irradiation by

high-activity ^{32}P radioactive stents may promote an 'atheromatous' neointima by the 6-month follow-up[11]. Controversially, in normal canine coronary arteries, radioactive stents result in a larger fibrin-rich neointima at follow-up, as compared to a control group[12].

In patients treated with implantation of ^{32}P radioactive stents with activities ranging from 0·75 to 12 μCi, angiographic restenosis was reported in 43–62% of the cases, with the restenosis primarily located at the edges of the stent[13]. The edges represent an area where tissue is subjected both to balloon-induced trauma and a lower dose of radiation, which may stimulate edge restenosis[9,14]. Our group reported that the implantation of a radioactive stent with an activity of 0·75 to 1·5 μCi was feasible and safe, with an in-stent restenosis rate of 17% and no occurrence of edge restenosis[14].

The aim of this study was to evaluate the safety and efficacy of implantation of a radioactive stent, with an activity level of 6-12 μCi, in patients with single, native, coronary artery disease.

Methods

Patient population

The European ^{32}P Dose Response Trial was a non-randomized multicentre trial to evaluate the safety and efficacy of radioactive stent implantation, with activities ranging from 1·5–3·0, 3–6 and 6–12 μCi. The data presented here is the experience of the Thoraxcenter Rotterdam.

Patients with single, native, coronary lesions, with a maximum lesion length of 28 mm (treatable with a maximum of two radioactive stents, implanted in tandem position), and objective evidence of ischaemia were eligible. Exclusion criteria were: recent myocardial infarction (creatine kinase-MB >three times the upper limit of normal, within 5 days of the intervention); left ventricular ejection fraction <40%; allergy or contraindication to aspirin, ticlopidine, clopidogrel or nickel; lesions located in the left main.

The Medical Ethical Committee of the University Hospital Rotterdam approved the study. All patients provided written informed consent before the procedure.

Radioactive stent, dosimetry and safety issues

The BX® Isostent (Isostent® Inc., San Carlos, CA, U.S.A.) was implanted in this trial. It was 15 mm in length and available in diameters of 3·0 and 3·5 mm. The BX® Isostent was made radioactive by Phosphorus-32 (^{32}P)[9]. The initial activity of the stents was measured and thereafter the date at which the radioactivity should have decreased to 6–12 μCi (radioactivity level suitable for implantation) was calculated. The dose delivered over 100 days at 1 mm from the stent surface was calculated for each implanted stent. All personnel were trained in the appropriate handling of radioactive materials. During implantation, the lucite shield enclosing the stent and the sheathed introduction system prevented exposure of the operator to the radiation of the stent. All disposable materials, which were in contact with the stent, were immediately disposed of in a plexiglas container.

Quantitative coronary angiography

Quantitative coronary angiography was performed pre-procedure, post-procedure, and at the 6-month follow-up. Coronary angiography was performed after intracoronary administration of nitrates. The off-line analysis of at least two orthogonal projections was performed by means of the CAAS II (Cardiovascular Angiographical Analysis System, Version II) (Pie Medical B.V., Maastricht, The Netherlands). Calibration of the system was based on dimensions of the catheters not filled with contrast medium, which has been extensively validated and applied in numerous clinical trials[15–17]. The following measurements were obtained in each projection for the target lesion: minimal luminal diameter, reference diameter, diameter stenosis and lesion length. Lesion length was measured by means of a computer algorithm[17]. Procedural success was defined as %diameter stenosis <20%, measured by on-line quantitative coronary angiography. Acute gain was defined as minimal luminal diameter post-procedure minus minimal luminal diameter pre-procedure. Late loss was defined as minimal luminal diameter post-procedure minus minimal luminal diameter at follow-up. The late loss index was defined as late loss divided by acute gain[18]. For analytical purposes, three regions of interest were defined: (1) stent area, (2) target lesion and (3) target vessel. The stent area was defined as the segment which included only the radioactive stent(s). The target lesion was defined as the stent area and 5 mm proximal and 5 mm distal to the edge of the radioactive stent. The target vessel was defined as the target lesion and the remaining segments of the treated vessel. Target lesion restenosis was defined as >50% diameter stenosis at follow-up, located within the target lesion. Edge restenosis was defined as >50% diameter stenosis at follow-up, located at the proximal and/or distal edge. In order to quantify an edge effect, a quantitative coronary angiography subsegmental analysis was performed in 30 patients, excluding patients with ostial lesions or occlusions pre-procedure or at follow-up. Target vessel stenosis was defined as >50% diameter stenosis at follow-up, located on any segment of the treated vessel. Quantitative coronary angiography measurements were performed by means of the CAAS II analysis system. Careful matching of the segments, encompassing the proximal and distal edges and the stent area, was performed pre-, post-procedure and at follow-up (see also Fig. 1).

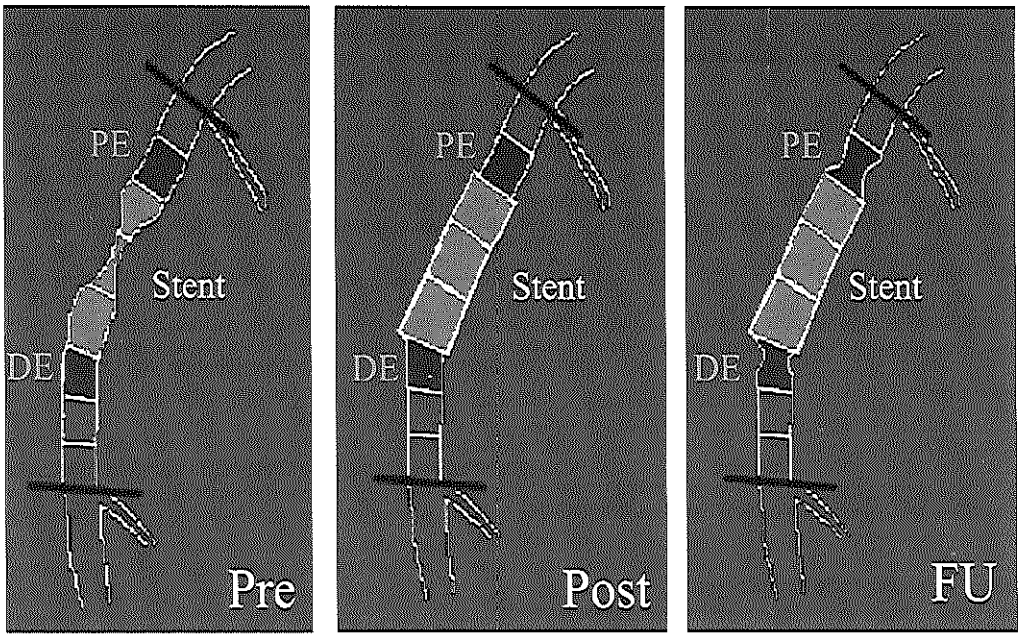

Figure 1 **Quantitative coronary angiography methodology. Quantitative coronary angiography measurements were performed at pre-procedure, post-procedure and follow-up. First, the Ref. diam. was measured from side-branch to side-branch (blue lines). Subsequently, the vessel was subdivided in segments of approximately 5 mm in length. Minimal lumen diameter, mean diameter and diameter stenosis were measured for the proximal edge, stent area and distal edge. DE=distal edge; FU=follow-up; PE=proximal edge; Pre=pre-procedure; Post=post-procedure; Stent=stent area.**

Procedure and follow-up

Patients received 250 mg aspirin and 10 000 international units heparin at the initiation of the procedure. The activation clotting time was maintained at >300 s. After balloon pre-dilatation, the radioactive stent was implanted at a nominal deployment pressure of 6–18 atmospheres. Extreme care was taken to minimize the trauma at both edges by taking the following, previously published[14], precautions: the best angiographic view to optimize stent visualization was chosen and the diaphragm was used to further enhance stent imaging. If needed, stent deployment was optimized using shorter post-dilatation balloons of larger diameter, to higher pressures. All post-dilatation balloons had a radio-opaque marker at each end. Images were filmed in a magnified field (5 inch), using digital zoom enhancement (3 inch) in order to avoid inflating the balloon outside the stent edges (see Table 1). All patients received either ticlopidine 250 mg twice daily or clopidogrel 75 mg daily for 3 months after stent implantation and aspirin 80 mg daily indefinitely. Creatinine kinase and creatine kinase-MB measurements were made and the electrocardiogram was recorded at 6 and 12–18 h post procedure in all patients.

Patients returned for a 1- and 5-month clinical follow-up. An electrocardiogram was recorded at each visit. Clinical end-points were: death, Q wave myocardial infarction (using the Minnesota code criteria[19]), non-Q wave myocardial infarction (creatine kinase-MB rise >twice normal upper limit), target lesion revascularization (reintervention of the stent area and/or revascularization of the proximal and distal edge), target vessel revascularization (revascularization of any segment of the treated vessel), non target vessel revascularization, subacute[20] and late[21] thrombotic occlusion of the target vessel. At the 5-month visit an exercise stress test was performed. Revascularization was performed on the basis of clinical symptoms and/or evidence of ischaemia on exercise testing.

Table 1 Balloon inflation and stent deployment data

	Pre-dilatation	Stent deployment	Post-dilatation
Nom. size balloon	3·09 ± 0·43	3·28 ± 0·25	3·51 ± 0·50
Balloon length	16 ± 3		14 ± 2*
Stent length		16 ± 3*	
Pressure	9 ± 4	10 ± 3	16 ± 2
Balloon artery ratio	1·06:1		1·17:1
Stent artery ratio		1·11:1	

*38 patients with one Isostent, two patients with two Isostents.

Table 2 Baseline patient demographics and anginal status

Gender	
Male	30 (75%)
Female	10 (25%)
Age (years)	
Average	58
Range	38–75
Risk factors	
Previous MI	20 (50%)
Diabetes mellitus	4 (10%)
Hyperlipidaemia	29 (73%)
Hypertension	18 (45%)
Smoking	14 (35%)
Family history	13 (33%)
Anginal class	
CCS 2	11 (27·5%)
CCS 3	23 (57·5%)
CCS 4	6 (15%)

MI=myocardial infarction; CCS=Canadian Cardiovascular Society.

Table 3 Baseline lesion characteristics

Treated vessel	
LAD	20 (50%)
LCx	10 (25%)
RCA	10 (25%)
Lesion type	
A	5 (12·5%)
B1	13 (32·5%)
B2	18 (45%)
C	4 (10%)
Ostial lesions	5 (12·5%)
Total occlusions	3 (8%)
Instent restenosis	2 (5%)
Lesion length	10 ± 3 mm

LAD=Left anterior descending coronary artery; LCx=left circumflex artery; RCA=right coronary artery.

Statistical analysis

Data are presented as mean ± standard deviation. Continuous data was compared by means of the two-tailed Student's t-test or linear regression when appropriate.

Results

Baseline characteristics

Baseline demographics and anginal state are shown in Table 2, lesion characteristics in Table 3.

Procedural data

All 42 stents were successfully implanted in 40 patients. Thirty-eight patients were successfully treated with a single radioactive stent, two required a second radioactive stent to cover lesions >15 mm. Eight patients received additional non-radioactive stents due to procedural dissections. There were three transient thrombotic occlusions during the procedure, two due to dissections and one due to a combination of a dissection with a low activation clotting time. Treatment was with Reopro in one patient and a combination of ReoPro and rtPA in the other two patients. Despite the Reopro and rtPA, one non-Q wave myocardial infarction occurred, leading to a maximum creatinine kinase of 673 IU . l^{-1} (normal upper limit 190 IU . l^{-1}) and an MB of 78 (normal upper limit 24 IU . l^{-1}). All further procedures were uncomplicated. A good final angiographical result was achieved in all patients.

Table 4 Five-month clinical follow-up

Angina free	26 (65%)
Target lesion revascularization	10 (25%)
PTCA	9 (22·5%)
CABG	1 (2·5%)
Target vessel revascularization	11 (28%)
Non-target vessel revascularization	1 (2·5%)
Late occlusion	2 (5%)
Myocardial infarction	1 (3%)
Death	0 (0%)

Follow-up

The mean hospital stay was 1·7 days. All patients were angina free at hospital discharge. At the 30-day follow-up no clinical end-points had occurred. Thirty-two (80%) patients were asymptomatic, whereas eight (20%) patients had recurrent angina pectoris. All 40 patients returned for the 5-month clinical follow-up (see Table 4). Twenty-six (65%) were asymptomatic and 14 (35%) patients had angina pectoris: Canadian Cardiovascular Society 1 (n=4), 2 (n=7), 3 (n=2) and 4 (n=1). The patient in angina Canadian Cardiovascular Society 4 had chest pain with ST-elevation, during his protocol-required 5-month exercise stress test. This was treated by primary angioplasty of a non-target vessel. Creatinine kinase rose to a maximum level of 257 IU . l^{-1} (normal upper limit 190 IU . l^{-1}) with an MB of 30 IU . l^{-1} (normal upper limit 24 IU . l^{-1}). Since there was neither a creatinine kinase rise of more than twice the upper limit of normal, nor new Q wave formation on the electrocardiogram, this was, by definition according to the protocol, not considered as a myocardial infarction.

A 5-month angiographic follow-up was performed in 36 (90%) patients. The remaining four (10%) patients refused; three were asymptomatic and the fourth had angina pectoris, Canadian Cardiovascular Society 3. Two late occlusions were noted, which were both proximal to the stent at angiographic follow-up. These two patients had recurrent angina >3 months after the index

Table 5 Quantitative coronary angiography analysis of the target lesion and stent area (n=36)*

	Pre	Post		Follow-up	
		Lesion	Stent	Lesion	Stent
MLD	0·98 ± 0·53	2·29 ± 0·52	2·57 ± 0·44	1·66 ± 0·71	2·12 ± 0·72
%DS	68 ± 15	28 ± 11	18 ± 11	46 ± 21	30 ± 21
Ref. diam.	3·07 ± 0·69	3·17 ± 0·53		3·03 ± 0·46	
Acute gain		1·31 ± 0·65	1·60 ± 0·59		
Late loss				0·63 ± 0·69	0·46 ± 0·76
LLI				0·65 ± 1·15	0·30 ± 0·53
Restenosis, n (%)				16 (44%)	0 (0%)

*Results of all 36 patients, who returned for angiographic follow-up, four patients refused.
%DS=% diameter stenosis; FU=follow-up; Lesion=target lesion (stent area and up to 5 mm proximal and distal to the stent edge); LLI=late loss index; MLD=minimal lumen diameter; Pre=pre-procedure; Post=post-procedure; Ref. diam.=reference diameter; Stent=stent area. Quantitative coronary angiography measurements are in mm.

procedure, more specifically: within 1 week of discontinuation of the clopidogrel, without any signs of a myocardial infarction. Sixteen (44%) patients (including the two total occlusions) had angiographic edge restenosis. There was no in-stent restenosis in the 34 patent vessels. Ten of the 16 restenoses occurred in patients treated with a single radioactive stent, two restenoses were in patients receiving two radioactive stents, four restenoses were observed in patients receiving a combination of one radioactive and one non-radioactive stent. Examining the four restenotic patients who had an additional non-radioactive stent implanted at the baseline procedure, one had a total occlusion proximal to the Isostent, therefore it cannot be established whether the BX-Isostent and the distally placed non-radioactive stent were patent. Of the remaining three patients, the restenoses all occurred at the edge, located contralateral to the non-radioactive stent (one implanted proximal and two implanted distal to the Isostent), whereas the non-radioactive stent had no restenosis. One of the two patients, treated with a radioactive stent for in-stent restenosis, had a restenosis at follow-up. This restenosis was located at the proximal edge. In the three patients treated initially for a total occlusion, one restenosis and one reocclusion occurred. Nine of the 16 restenotic patients underwent a target lesion re-PTCA, one patient was referred to bypass surgery because it was the third in-stent restenosis in this patient, the remaining six were treated medically since these patients were both asymptomatic and had a negative stress test.

Quantitative coronary angiography measurements

Quantitative coronary angiography data, as measured for the target lesion and stent area, are presented in Table 5. Results of the subsegmental analysis of the stent area and the edges in a subgroup of 30 patients are shown in Table 6. Location of the restenosis is summarized in Table 7. Restenosis was observed to occur more often at the proximal edge compared to the distal edge (P=0·02).

Table 6 Subsegmental analysis of the stent area and edges (subgroup of 30 patients)*

	Prox. edge	Stent area	Dist. edge
MLD			
Pre	2·52 ± 0·81	1·09 ± 0·48	2·33 ± 0·70
Post	2·81 ± 0·53	2·57 ± 0·46	2·37 ± 0·63
FU	2·05 ± 0·71	2·26 ± 0·52	2·07 ± 0·63
%DS			
Pre	17 ± 10	55 ± 16	13 ± 6
Post	9 ± 4	17 ± 8	13 ± 8
FU	22 ± 13	22 ± 12	16 ± 12
Mean. diam.			
Pre	2·99 ± 0·79	2·45 ± 0·78	2·68 ± 0·80
Post	3·09 ± 0·55	3·10 ± 0·43	2·70 ± 0·58
FU	2·57 ± 0·60	2·89 ± 0·58	2·44 ± 0·57
Acute gain	0·29 ± 0·69	1·47 ± 0·52	0·04 ± 0·61
Late loss	0·76 ± 0·66	0·31 ± 0·56	0·30 ± 0·66
LLI	NA	0·23 ± 0·46	NA
Restenosis rate, n (%)	10 (33%)	0 (0%)	5 (17%)

*Excluded from subsegmental analysis were two patients with ostial lesions, one patient with a total occlusion pre-procedure and three patients with total occlusions at follow-up.
%DS=% diameter stenosis; Dist. edge=distal edge; FU=follow-up; LLI=late loss index; Mean. diam.=mean diameter; MLD=minimal lumen diameter; NA=not applicable; Prox. edge=proximal edge; Pre=pre-procedure; Post=post-procedure. QCA measurements are in mm.

Table 7 Location of the restenosis (n=16)

Proximal edge	9 (56%)
Distal edge	4 (25%)
Proximal and distal edges	1 (6%)
Stent area	0 (0%)
Unknown (proximal occlusion)	2 (13%)

Radiation doses

Stent activity level was 8·6 ± 1·6 μCi at implantation, resulting in a calculated cumulative dose given over 100 days delivered to a 1 mm depth from the stent surface of 58 ± 10 Gy. There was no correlation between stent activity or delivered dose and minimal luminal diameter or late loss index at follow-up.

Discussion

This non-randomized study illustrates that the implantation of a 6–12 μCi β-particle emitting radioactive stent is safe and feasible, with one procedural non-Q wave myocardial infarction and no subacute or 30-day clinical events recorded. Subacute thrombosis was not seen despite the concern of delay in endothelialization, as previously reported in animal studies[8,10]. Two late occlusions were seen, which were probably late thrombotic stent occlusions, since both patients had recurrent angina, within 1 week of discontinuation of the clopidogrel. However, since both occlusions were proximal to the stent, and stent patency could not be observed at angiography, severe edge restenosis cannot be fully excluded. Therefore, it may be desirable to give patients at least 6 months of clopidogrel following radioactive stent implantation.

The Milan group has previously reported restenosis not only within the stent, but also at the edges of the stent[13], possibly caused by a combination of balloon injury (barotrauma) and lower radiation dose at the stent edges[9,14]. In this series particular attention was paid to avoid balloon injury outside the stent, in order to minimize barotrauma at the edges. Despite these precautions, edge restenosis was seen in 44%, occurring predominantly at the proximal edge. The commonly occurring narrowing observed proximal to the edge of the stent may, in combination with a complete inhibition of neointimal proliferation inside the stent, create unfavourable rheological conditions, such as a diverging flow pattern, which in itself will self-perpetuate the neointimal proliferation[22]. Careful shear stress analysis could elucidate the cause of restenosis at the proximal edge[23].

Since in all cases the pre-dilatation was performed with a balloon longer than the BX-Isostent and the balloon used for stent deployment extended outside the edges of the stent, geographical 'miss' occurred in 100% of the cases. Since geographical miss has been shown to be one of the determinants of edge restenosis[24], future therapies will concentrate on the prevention of geographical miss by minimizing trauma and/or increasing radiation dose at the edges. Several new therapies are currently under investigation. Direct stenting will prevent trauma caused by pre-dilatation with balloons longer than the radioactive stent. Square shouldered balloons, used for stent deployment, in which the entire balloon remains within the stent, will minimize barotrauma at the proximal and distal edges. Cold end stents, in which the centre of the stent is made radioactive, while the proximal and distal 5 mm of the stent edges are non-radioactive may prevent edge restenosis, if this restenosis is caused by negative remodelling. The final therapeutic option is the implantation of hot end stents, in which the stent edges are made more radioactive compared to the centre of the stent. This strategy increases the dose delivered to the traumatized proximal and distal edge, thereby decreasing the chance of geographical miss[22].

Conclusion

These results indicate that the use of radioactive stents, with an activity of 6–12 μCi, is safe and feasible; however, the high incidence of edge restenosis makes this technique currently clinically non-applicable.

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Part 3

Mechanisms & side effects.

Chapter 5

Positive geometric vascular remodeling is seen after catheter-based radiation followed by conventional stent implantation but not after radioactive stent implantation.

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Positive Geometric Vascular Remodeling Is Seen After Catheter-Based Radiation Followed by Conventional Stent Implantation but Not After Radioactive Stent Implantation

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Background—Recent reports demonstrate that intracoronary radiation affects not only neointimal formation but also vascular remodeling. Radioactive stents and catheter-based techniques deliver radiation in different ways, suggesting that different patterns of remodeling after each technique may be expected.

Methods and Results—We analyzed remodeling in 18 patients after conventional stent implantation, 16 patients after low-activity radioactive stent implantation, 16 patients after higher activity radioactive stent implantation, and, finally, 17 patients who underwent catheter-based radiation followed by conventional stent implantation. Intravascular ultrasound with 3D reconstruction was used after stent implantation and at the 6-month follow-up to assess remodeling within the stent margins and at its edges. Preprocedural characteristics were similar between groups. In-stent neointimal hyperplasia (NIH) was inhibited by high-activity radioactive stent implantation (NIH 9.0 mm^3) and by catheter-based radiation followed by conventional stent implantation (NIH 6.9 mm^3) compared with low-activity radioactive stent implantation (NIH 21.2 mm^3) and conventional stent implantation (NIH 20.8 mm^3) ($P=0.008$). No difference in plaque or total vessel volume was seen behind the stent in the conventional, low-activity, or high-activity stent implantation groups. However, significant increases in plaque behind the stent (15%) and in total vessel volume (8%) were seen in the group that underwent catheter-based radiation followed by conventional stent implantation. All 4 groups demonstrated significant late lumen loss at the stent edges; however, edge restenosis was seen only in the group subjected to high-activity stent implantation and appeared to be due to an increase in plaque and, to a lesser degree, to negative remodeling.

Conclusions—Distinct differences in the patterns of remodeling exist between conventional, radioactive, and catheter-based radiotherapy with stenting. (***Circulation.*** **2000;102:1434-1439.)**

Key Words: stents ■ remodeling ■ radioisotopes ■ angioplasty ■ ultrasonics

In our enthusiasm to control vessel recoil and remodeling after balloon angioplasty (BA), stent implantation has become increasingly popular. With conventional stenting, we have eliminated recoil and remodeling as components of the restenotic process. However, this has been at the cost of exacerbating neointimal proliferation secondary to chronic vessel wall irritation, leading to in-stent restenosis.[1,2]

Intracoronary radiation has been developed in an attempt to decrease restenosis after BA and stent implantation. Two parallel technologies, one using radioactive stents[3–7] and the other using catheter-based radiation,[8–10] have been the subject of both animal and human studies. Given the different dose rates and total doses delivered by each method, one may intuitively expect different patterns of remodeling subsequent to each approach.

Whereas the effect of catheter-based radiation after BA on vascular remodeling has been described,[11] the response of the arterial wall to catheter-based radiation and subsequent stent implantation has not been described. Preliminary studies have reported the effect at the stent edge after radioactive stent implantation.[4] However, these reports did not encompass the response behind the stent in the arterial wall.

The aim of the present study was to describe the response of the coronary artery to radiation and stenting by examining the stent and its edges after radioactive stent implantation and also after catheter-based radiation with stent implantation.

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TABLE 1. Clinical Characteristics

	Groups			
	C	LA	HA	CBS
Patients, n	18	16	15	17
Age, y	58 (42–76)	60 (43–74)	59 (42–75)	57 (45–74)
Male, %	70	66	70	60
Prior MI, %	40	40	45	40
Unstable angina, %	60	50	65	55
Smoking, %	40	55	40	40
Hypercholesterolemia, %	60	62	65	55
Family history, %	33	42	30	40
Hypertension, %	40	42	30	33
Diabetes, %	5	5	10	6

Age values are mean (range). MI indicates myocardial infarction.

Methods

Patient Selection

We analyzed geometric vascular remodeling in 4 groups of patients: (1) LA group, those who had undergone implantation of ^{32}P-emitting radioactive stents at activity levels of 0.75 to 1.5 μCi (Isostent Inc); (2) HA group, those who had undergone implantation of ^{32}P radioactive stents at activity levels of 6.0 to 12 μCi (Isostent Inc); (3) CBS group, those who had undergone conventional stent implantation after suboptimal BA (clinically significant dissection or residual stenosis >30%) and catheter-based radiation; and (4) C group, those who had undergone conventional stent implantation after suboptimal BA .

Stents analyzed were from patients with single–native-vessel coronary artery disease, normal left ventricular function, and objective evidence of ischemia. All groups were matched for patient baseline characteristics, vessel size, lesion, and stent length. Stents placed in the ostial position or adjacent to major side branches, such that the stent edges were unable to be analyzed, were excluded from analysis. Only patients who had completed 6-month angiographic and intravascular ultrasound (IVUS) follow-up were included.

Implantation Technique

The same group of cardiologists, using a similar technique, implanted all stents. Predilation of the lesion was performed, followed by stent implantation with use of either a premounted stent or the Johnson & Johnson delivery system (Johnson & Johnson Interventional Systems Co). A balloon shorter than the stent was then selected, and high-pressure balloon inflation was performed within the stent to ensure good stent apposition. Intravascular ultrasound was used to ensure optimal stent deployment.

Medication

Patients received 250 mg aspirin and 10 000 IU heparin at the initiation of the procedure, and the activated clotting time was maintained at >300 seconds. All patients received aspirin (80 mg daily) indefinitely and ticlopidine (250 mg BID) for 2 weeks (C group) or clopidogrel (75 mg daily) for 12 weeks (LA, HA, and CBS groups) after stent implantation.

Radioactive Stents

The BX stent (Isostent Inc) was the only radioactive stent implanted in this trial. It was 15 mm in length and available in diameters of 3.0 and 3.5 mm. The BX stent was made radioactive by ^{32}P. The initial activity of the stents was measured; thereafter, it was calculated at the date on which the activity had decreased to 0.75 to 1.5 μCi or 6 to 12 μCi, levels suitable for implantation.

Catheter-Based Radiation Delivery System

The Beta-Cath System (Novoste Corp) was used to deliver localized β-radiation (^{90}Sr/^{90}Y) to a depth of 2 mm from the center of the

TABLE 2. Procedural Characteristics

	Groups			
	C	LA	HA	CBS
Vessels, n				
LAD	10	9	9	9
LCx	4	3	3	4
RCA	4	4	3	4
Lesion length, mm	9.6±3.3	12.1±3.8	10.1±3.3	11.9±4
Stent length, mm	14.6±3.8	15.0	15.0	15.2±4.1
Balloon length after implantation, mm	14.8±3.4	14.4±2.8	14.1±2.6	15.1±3.6
Final balloon size, mm	3.2±0.4	3.1±0.6	3.4±0.5	3.2±0.5
Max inflation pressure 1	11.5±2.4	11.6±2.6	10.2±2.8	12.2±2.6
Max inflation pressure 2	14.6±3.2	15.2±2.4	15.8±1.7	15.4±3.3
Balloon-to-artery ratio	1.04±0.05	1.12±0.06	1.10±0.06	1.12±0.05

Values are mean±SD. LAD indicates left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; Max inflation pressure 1, balloon at time of stent implantation; and Max inflation pressure 2, balloon inflation within stent.

TABLE 3. Volumes for Edge Proximal and Distal to Stent (10-mm Length)

	Edge, mm^3					
	LV		TVV		Plaque	
Group	Post	F/UP	Post	F/UP	Post	F/UP
C	67.7±18.9	58.3±19.3*	124.4±32.6	116.5±34.1*	56.7±22.6	58.2±23.1
LA	75.2±39.0	67.3±34.4*	126.6±58.0	116.4±49.0*	51.4±24.5	49.1±21.0
HA	74.9±23.0	63.0±23.7*	126.2±44.9	117.6±46.2*	51.3±16.4	54.6±16.1
CBS	72.6±27.7	61.1±26.3*	133.2±48.5	138.9±46.5†	60.6±26.1	77.8±28.6*†

Values are mean±SD. Post indicates baseline; F/UP, follow-up.
*$P<0.05$ vs Post (within-group comparison); †$P<0.05$ for between-group comparison (ANOVA).

source at the site of coronary intervention. The device consisted of 3 components: (1) the transfer device that stored the radiation source train and allowed the positioning of these sources within the catheter; (2) the delivery catheter, which was a 5F multilumen over-the-wire noncentered catheter that used saline solution to send and return the radiation source train; and (3) the radiation source train, which consisted of a series of 12 independent cylindrical seeds that contained the radioisotope ^{90}Sr sources and was bordered by 2 gold radiopaque markers separated by 30 mm. Other device and procedural details have been previously published by this group.[11]

Definitions

Stent Edges

Stent edges were defined as those volumes axially 5 mm proximal and distal to the final stent strut. An edge restenosis was defined as an angiographic restenosis >50% at 6-month follow-up located at either stent edge. An edge effect was defined as any stent-edge renarrowing.

Patients with balloon-injured edges that failed to receive radiation in the catheter-based radiation group were excluded. In other words, no stents implanted in areas of geographical miss were included in the present study.

IVUS Image Acquisition Analysis

After the final balloon inflation and administration of intracoronary nitrates, ECG-gated IVUS pullback was performed. This was repeated at the 6-month follow-up.

The segment subjected to 3D reconstruction was examined with a mechanical IVUS system (ClearView, CVIS) with a sheath-based IVUS catheter incorporating a 30-MHz single-element transducer rotating at 1800 rpm. The IVUS transducer was withdrawn through the stationary imaging sheath by an ECG-triggered pullback device with a stepping motor.[12] IVUS images coinciding with the peak of the R wave, which eliminates the artifacts caused by the movement of the heart during the cardiac cycle, were acquired. After each image acquisition, the transducer was withdrawn 0.2 mm to acquire the next image coincident with the R wave. The ECG-gated image acquisition and digitization was performed by a workstation designed for the 3D reconstruction of echocardiographic images[12] (EchoScan, Tomtec). A Microsoft Windows–based contour detection program, developed at the Thoraxcenter, Rotterdam, was used for the automated 3D analysis of up to 200 IVUS images.[13] The feasibility, reproducibility, and interobserver and intraobserver variability of this system have been previously validated in clinical protocols.[11]

Quantitative IVUS Analysis

At the stent edges, the area encompassed by the lumen-intima and media-adventitia boundaries defined the luminal volume (LV) and the total vessel volume (TVV), respectively. The difference between LV and TVV defined the plaque volume. TVV, stent volume, neointimal hyperplasia (NIH), plaque behind the stent (TVV−stent volume), and LV were obtained within the axial boundaries of the stent.

The assessment of TVV in stented patients has previously been reported.[14] Although in the previous report the delineation of TVV was not possible in some patients because of stent shadowing, in the present study the delineation of the TVV boundary was possible in all stented patients. When the TVV boundary was not visible in a single cross-sectional view, the computer extrapolated it from the contours of the previous and subsequent cross sections. In addition, the use of 3D reconstruction with multiple longitudinal views facilitates the visualization of vessel structures outside the stent.

Statistical Analysis

Quantitative data are presented as mean±SD. Volumetric data derived from the 3D reconstruction of the IVUS imaging were compared immediately after treatment and at follow-up by the 2-tailed paired Student *t* test. Comparison between groups was performed by 1-way ANOVA. A value of $P<0.05$ was considered statistically significant.

The Medical Ethical Committee of the University Hospital Rotterdam approved the study, and all patients provided written informed consent before the procedure.

TABLE 4. Volumes for Stent

	Stent, mm^3						
	LV		TVV		PBS		
Group	Post	F/UP	Post	F/UP	Post	F/UP	NIH
C	113.9±29.7	92.8±28.7*	256.1±73.2	257.3±67.4	142.2±54.1	143.7±49.4	20.8±11.5
LA	127.3±42.6	105.5±40.1*	266.6±96.5	264.5±98.3	139.3±59.1	137.8±63.7	21.2±12.1
HA	122.4±20.0	111.7±24.3*	267.8±66.9	265.3±65.1	145.4±49.1	144.6±45.3	9.0±8.6†
CBS	128.6±41.3	121.8±41.6*	258.9±73.6	278.0±89.8*	130.3±34.2	149.3±49.8*	6.9±6.6†

Values are mean±SD. Post indicates baseline; F/UP, follow-up; and PBS, plaque behind the stent. No significant difference between groups was seen at baseline (Post).
*$P<0.05$ vs Post (within-group comparison); †$P<0.05$ for between-group comparison (ANOVA).

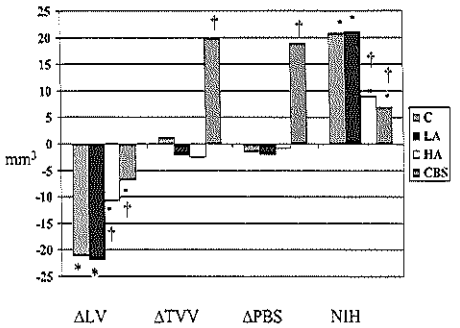

Figure 1. Remodeling within margins of stent. PBS indicates plaque behind the stent. *P<0.05 for values immediately after treatment vs follow-up; †P<0.05 for values between groups.

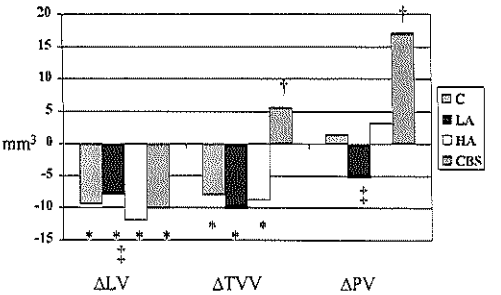

Figure 2. Changes in volumes at stent edge. PV indicates plaque volume. *P<0.05 for values immediately after treatment vs follow-up; †P<0.05 for values between groups; and ‡P=NS for ΔLV (all groups) and ΔPV (C, LA, and HA groups).

Results

Baseline Characteristics

Eighteen patients were enrolled in the conventional group (C group), 16 patients were enrolled in both the 0.75- to 1.5-μCi and the 6.0- to 12-μCi radioactive stent groups (LA and HA groups, respectively), and 17 patients were enrolled in the group subjected to catheter-based radiation plus a stent (CBS group). In the C group, 10 ACS Multi-Link (Guidant Corp) and 8 NIR (new intravascular rigid-flex stent; Boston Scientific/Scimed) stents were implanted, and in the CBS group, 8 NIR and 9 ACS Multi-Link stents were implanted. Baseline characteristics are similar between all groups and are described in Table 1. Lesion and procedural characteristics are described in Table 2. No statistically significant differences were seen between groups in the parameters described in Table 2. Comparisons of volumetric data measured at the stent edges and within the margins of the stent are presented in Tables 3 and 4.

In-Stent Inhibition of NIH

Intrastent NIH was decreased after high-activity radioactive stent implantation and catheter-based radiation followed by conventional stent implantation (P=0.008). Lower activity radioactive stents had an effect similar to that of conventional stent implantation (see Table 4 and Figure 1).

Behind Stent

The C, LA, and HA groups demonstrated an absence of remodeling behind the stent, with no significant changes in TVV or plaque volumes. This is in contrast to the CBS group, which demonstrated a significant increase in plaque (immediately after treatment versus follow-up, 15%; P=0.002) and an increase in TVV (after treatment versus follow-up, 8%; P=0.003). Intergroup comparison showed that this change was significant (Table 4, P=0.01). Further comparisons of changes within and between groups are demonstrated in Figure 1. No chronic recoil of the stent was seen in any group.

Stent Edge

No significant difference between groups was seen at baseline (after stent implantation). All groups demonstrated late lumen loss at the stent edges. At the stent edges, remodeling is similar in the C and LA groups. In these groups, there is evidence of a decrease in TVV, with little change in plaque as a cause of late lumen loss (Figure 2). In the HA group, a target segment restenosis (angiographically >50%) was observed in 7 patients at the stent edges. This was more common at the proximal edge (in 6 of 7 patients). The major mechanism of such a restenosis appears to be due to an increase in plaque at the stent edge. In nonrestenotic patients, the edge effect appears to be due to a decrease in TVV and, to a lesser degree, an increase in plaque (Figure 3).

In the CBS group, the edge effect is largely due to an increase in plaque, with no negative remodeling seen (P=0.045 for plaque increase in CBS versus LA, HA, and C groups). No patient with edge restenosis after catheter-based radiation was seen in our series of patients.

Stent Activity and Dose Prescribed

Mean stent activity at implantation (LA group) was 1.1±0.3 μCi. Mean stent activity at implantation (HA group) was 8.6±1.6 μCi. For the CBS group, the mean dose prescribed was 16.7±2.0 Gy.

Discussion

The development of NIH within the stent witnessed at the 6-month follow-up is well appreciated[15]; however, the

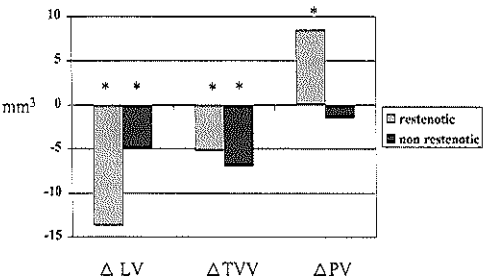

Figure 3. High-activity (6.0- to 12.0-μCi) stents. Restenotic edges are compared with nonrestenotic edges. Δ indicates change in volume (immediately after treatment vs follow-up). *P<0.05 for values immediately after treatment vs follow-up. Note greater lumen loss seen in restenotic group. This loss was caused by increase in plaque (P<0.05) and a less profound decrease in TVV (P<0.05). ΔTVV is similar in both groups.

changes that occur at the stent edges or indeed behind the stent struts have not been the focus of attention until recently.[4] The present study is the first to describe the difference in vascular remodeling seen after radioactive stent implantation and catheter-based radiation plus stenting with the use of modern conventional stents as a benchmark. The key findings are as follows: (1) The degree of inhibition of NIH was similar in the HA and CBS groups. (2) There was no significant remodeling behind the stent after conventional or radioactive stent implantation; however, the CBS group demonstrated an increase in plaque behind the stent and in TVV. (3) At the stent edge, 3 patterns of remodeling are seen at the 6-month follow-up: first, a shrinkage in TVV and LV was noted in the C and LA groups. These 2 subgroups were not associated with stent edge restenosis in this series. After high-activity stent implantation, a pattern similar to conventional and low-activity stent implantation is seen in those edges that remain nonrestenotic; however, in the restenotic edges, plaque increase is the major contributor to lumen loss. In the CBS group, a lumen loss similar to that found in the other groups is seen; however, this occurs secondary to a relatively greater increase in plaque, without loss in TVV.

Neointimal Hyperplasia

In the present study, neointimal formation was inhibited after higher dose radioactive stent implantation and after catheter-based radiation plus stenting. The present study is in contrasts to the recent study by Carter et al,[16] who used ^{32}P stents in the porcine model, but is in keeping with earlier studies of Hehrlein et al,[6] who used the rabbit model, and recent reports by Albiero et al,[4] who noted a dose-dependent inhibition of NIH.

Mechanism of Remodeling Behind the Stent

Catheter-Based Radiation

After conventional and radioactive stent implantation, little positive or negative remodeling is witnessed behind the stent. In stark contrast to this is the increase in plaque behind the stent and TVV seen after catheter-based radiation and stenting. Part of the key to understanding this process may be acquired from understanding the healing process after BA. Wilcox and colleagues[17,18] describe the presence of early proliferation of myofibroblasts expressing contractile proteins in the adventitia surrounding the porcine coronary artery after BA. Tracing studies have indicated that the same cells migrate and form part of the neointima. Wilcox and colleagues hypothesize that the adventitial myofibroblasts constrict the artery at the angioplasty site in much the same way as myofibroblasts participate in scar retraction in dermal healing. The source of these myofibroblasts may be distant to the immediate site of injury, including pericardial, adipose, and intramyocardial layers.[19]

Radiation treatment of porcine coronary arteries after BA upregulates p21 synthesis in adventitial cells, especially myofibroblasts. Such induction is dose dependent and is sustained for at least 7 days after radiation. Additionally, radiation inhibits the expression of growth factors, reduces the proliferation of adventitial myofibroblasts, and decreases the production of α-actin by the adventitial myofibroblasts, preventing the formation of the myofibroblast scar around the angioplasty site and negative vascular remodeling.[17,20] Data from Fareh and et al [21] suggest that inhibition of migration but not of cellular proliferation may occur at lower doses of radiation. Therefore, cells may remain in situ, unable to migrate but able to grow in the presence of a weakened external elastic membrane. After 1 week, the effect of the radiation diminishes, and cellular proliferation, possibly as a reaction to the presence of the stent, continues behind the stent in the context of positive vascular remodeling. In our cohort of patients, no cases of stent malapposition were seen at follow-up, although our group has described this as a risk of ongoing positive vascular remodeling.[22,23] A further concept to be explored is that relating to the sharp drop-off in radiation seen with the β-radiation source, which may cause underdosing deep in the adventitia and geographical miss[24] in a radial sense rather than the more commonly described longitudinal sense.

Radioactive Stent

The objective of using the radioactive stent is not to neutralize myofibroblasts in the adventitia; it is the prevention of the migration and invasion of myofibroblasts from the adventitia through the stent struts and into the lumen. As is seen in the HA group, this is accomplished by the continuous and low dose rate provided by the radioactive stent. Because of the range of the "radioactive fence" created, adventitial cells remain intact without upregulation of growth factors and inhibition of contractile proteins. Consequently, no remodeling is seen behind the radioactive stent at either activity level.

Edge Remodeling

Hoffmann et al[15] have previously described negative remodeling at the stent edge after conventional stent implantation. In the present study, we have been able to precisely describe the decrease in TVV as the dominant contributor to nonrestenotic lumen loss at the stent edge. Recent reports on radioactive stents suggest that the edge effect and edge restenosis may be due to an increase in plaque at the edge and to a component of negative remodeling as one moves axially from the stent.[4] The contributing factors to radioactive stent edge restenosis have been discussed in detail recently by Serruys and Kay.[25]

It may be argued that stent-edge restenosis was not seen in the CBS group because no individuals with geographical miss were evaluated. However, our objective in the present study was to analyze the vascular response to appropriately applied catheter-based radiation, which necessitates the exclusion of all those in whom injury was not covered by radiation. Recent reports have suggested that the combination of suboptimal low-dose radiation and injury may make individuals with geographical miss vulnerable to edge restenosis.[26]

Study Limitations

This was a retrospective nonrandomized study of individuals who had completed 6 months of follow-up and in whom IVUS examination was possible. Individuals who had a total occlusion or in whom the IVUS catheter could not be passed under acceptable clinical circumstances were not included.

No edge restenosis was seen in the CBS group, unlike the HA group; however, both the CBS and the HA groups reflected the larger parent populations from which they were selected in all other features.

The dosimetry (catheter-based) described in the present study relates to prescribed doses only and does not necessarily reflect the dose delivered 2 mm from the source in the adventitia. Description of dosimetry is beyond the scope of the present study; however, previous work by the authors (Sabaté et al[27]), who used a similar radiation source and study population, suggests that delivered dose, residual plaque burden, and tissue composition play a fundamental role on the volumetric outcome at 6 months of follow-up after catheter-based β-radiation therapy and BA.

Conclusions

Distinct differences in the patterns of remodeling exist between conventional, radioactive, and catheter-based radiotherapy with stenting. Users of radiation need to be alerted to edge restenosis seen after higher activity radioactive stent implantation and positive remodeling behind the stent seen after catheter-based radiation and stenting. Radiation, whether it be catheter or stent-based, has forced the interventional community to look closely not only at effective inhibition of intimal proliferation but also at the adverse response of the artery to the combination of injury and radiation.

Acknowledgments

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Chapter 6

The pattern of restenosis and vascular remodeling after cold-end radioactive stent implantation.

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The pattern of restenosis and vascular remodelling after cold-end radioactive stent implantation

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Background Edge restenosis is a major problem after radioactive stenting. The cold-end stent has a radioactive mid-segment (15·9 mm) and non-radioactive proximal and distal 5·7 mm segments. Conceptually this may negate the impact of negative vascular remodelling at the edge of the radiation.

Method and Results ECG-gated intravascular ultrasound with three-dimensional reconstruction was performed post-stent implantation and at the 6-month follow-up to assess restenosis within the margins of the stent and at the stent edges in 16 patients. Angiographic restenosis was witnessed in four patients, all in the proximal in-stent position. By intravascular ultrasound in-stent neointimal hyperplasia, with a >50% stented cross-sectional area, was seen in eight patients. This was witnessed proximally (n=2), distally (n=2) and in both segments (n=4). Echolucent tissue, dubbed the 'black hole' was seen as a significant component of neointimal hyperplasia in six out of the eight cases of restenosis. Neointimal hyperplasia was inhibited in the area of radiation: Δ neointimal hyperplasia=3·72 mm^3 (8·6%); in-stent at the edges of radiation proximally and distally Δ neointimal hyperplasia was 7·9 mm^3 (19·0%) and 11·4 mm^3 (25·6%), respectively (P=0·017). At the stent edges there was no significant change in lumen volume.

Conclusions Cold-end stenting results in increased neointimal hyperplasia in in-stent non-radioactive segments.

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Key Words: Stents, remodelling, radioisotopes, angioplasty, ultrasonics.

See page 1245 for the Editorial comment on this article

Introduction

Conventional stenting has eliminated recoil and negative remodelling as components of the restenotic process. However, this has been at the cost of exacerbating neointimal proliferation secondary to chronic vessel wall irritation, leading to in-stent restenosis[1,2].

Intracoronary radiation has been developed in an attempt to decrease restenosis after balloon angioplasty and stent implantation. Studies recently performed in humans demonstrated a dose-dependent inhibition of neointimal hyperplasia at the 6-month follow-up in stents with activity levels >3 μCi[3,4]. However, a significant increase in neointimal hyperplasia was noted at the extremes of the stent and at the edges. Edge restenosis was mainly due to an increase in plaque and to a lesser extent, remodelling of the native vessel wall[4,5]. A fall-off in radiation in areas receiving vascular injury was proposed as a possible stimulatory mechanism. In order to minimize the effect of vascular remodelling on stent-edge restenosis, the stent design was modified. The 'cold-end' stent (Isostent® Inc., San Carlos, CA, U.S.A.) was rendered radioactive in its mid-portion (15·9 mm in length); the edges (5·7 mm each) were non-radioactive (Fig. 1).

We aimed to analyse tissue growth within the stent and at its edges and to define the segments that had the greatest propensity to restenosis after the implantation of a cold-end stent.

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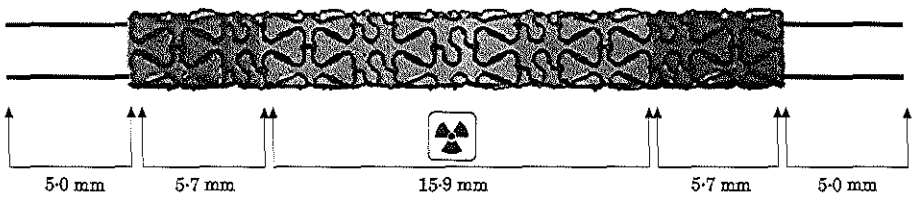

Figure 1 **A cold-end stent with a central radioactive segment and proximal and distal non-radioactive segments. Analysis of each segment was performed individually to assess neointimal hyperplasia. This included neointimal hyperplasia over the length of the stent and edges.**

Methods

Patient selection

We analysed neointimal hyperplasia and vascular remodelling in 16 patients who had completed a 6-month angiographic follow-up with intravascular ultrasound analysis. All patients had single native vessel coronary artery disease, normal left ventricular function and objective evidence of ischaemia.

Implantation technique

Pre-dilation of the lesion was performed where necessary followed by stent implantation High-pressure balloon inflation to ensure good strut apposition to the vessel wall was then performed at the operator's discretion. At this time we used a shorter balloon to ensure that the edges of the balloon did not extend beyond the limits of the stent[3]. Intravascular ultrasound was used to ensure optimal stent deployment.

Medication

Patients received 250 mg aspirin and 10 000 international units of heparin at the initiation of the procedure and the activated clotting time was maintained at >300 s. All patients received aspirin 80 mg daily indefinitely and clopidogrel 75 mg daily for 6 months.

Radioactive stent

The stent was 27·3 mm in length and available in diameters of 3·0 and 3·5 mm. It was made radioactive in its central portion by phosphorus-32 (^{32}P)[3]. The 5·7 mm edges were shielded from radiation. The initial activity of the stents was measured and thereafter it was calculated at what date the activity had decreased to 3·0–12·0 μCi, suitable for implantation.

Intravascular ultrasound image acquisition analysis

After the final balloon inflation and administration of intracoronary nitrates, ECG-gated intravascular ultrasound pullback was performed. This was repeated at the 6 month follow-up. The segment was subjected to three-dimensional reconstruction and examined with a mechanical intravascular ultrasound system (Clearview, CardioVascular Imaging System, Sunnyvale, CA, U.S.A.) with a sheath-based intravascular ultrasound catheter incorporating a 30 MHz single-element transducer rotating at 1800 rpm. The intravascular ultrasound transducer was withdrawn through the stationary imaging sheath by an ECG-triggered pullback device with a stepping motor[6]. Intravascular ultrasound images were acquired, coinciding with the peak of the R wave, which eliminates the artefacts caused by the movement of the heart during the cardiac cycle. After each image acquisition, the transducer was withdrawn 0·2 mm to acquire the next image coincident with the R-wave. By definition, this permits acquisition of five slices per mm, enabling the operator to easily define the stent margins. By increasing the frequency of sampling this approach may also decrease error due to regression to the mean created by the use of greater step sizes and non-ECG-gating[7,8].

ECG-gated image acquisition and digitation was performed using a workstation designed for three-dimensional reconstruction of echocardiographic images[6] (EchoScan, Tomtec, Munich, Germany). A Microsoft Windows®-based contour detection program, developed at the Thoraxcenter, was used for automated three-dimensional analysis of up to 200 intravascular ultrasound images[9]. This program constructs two longitudinal sections and identifies the contours corresponding to the lumen–intima and media–adventitia boundaries, using a minimum-cost based software algorithm. The feasibility, reproducibility and the inter- and intra-observer variability of this system have been previously described in clinical protocols[5,9].

Quantitative intravascular ultrasound analysis

At the stent edges, the area encompassed by the lumen–intima and media–adventitia boundaries defined the luminal and the total vessel volumes, respectively. The difference between luminal and total vessel volumes defined the plaque volume. Within the boundaries of the stent total vessel volume, stent volume, neointimal hyperplasia, and lumen volumes were obtained. The

neointimal hyperplasia presented was a value measured at follow-up (stent volume–lumen volume).

The assessment of total vessel volume in stented patients has previously been reported[5,10]. In our study the delineation of the total vessel volume boundary was possible in all stented patients. When the total vessel volume boundary was not visible in a single cross-sectional view, the computer extrapolated it from the contours of the immediately previous and following cross-sections. In addition, the use of three-dimensional reconstruction with multiple longitudinal views, facilitates the visualization of vessel structures outside the stent.

Definitions and segments of analysis

Stent edges were defined as those volumes axially 5 mm proximal and distal to the final stent strut. In addition, segments in-stent proximally and distally were analysed separately to assess neointimal hyperplasia in areas which were subject to injury and received stent implantation. Effectively, these were segments which received a fall-off in radiation. Finally the in-stent radioactive segment was analysed (see Fig. 1). To facilitate comparison between the non-radioactive in-stent segments (5·7 mm) and the central radioactive segment (15·9 mm), lengths were normalized to a standard length (5 mm) and appropriate comparisons made. Restenosis was defined as an angiographic restenosis >50% at 6-month follow-up, by off-line quantitative coronary angiography.

Statistical analysis

Quantitative data are presented as mean ± standard deviation. Volumetric data derived from the three-dimensional reconstruction of the intravascular ultrasound image were compared immediately after treatment and at follow-up using the two-tailed paired Student's t-test. ANOVA was used to compare multiple variables. A value of $P<0·05$ was considered statistically significant.

The Medical Ethical Committee of the University Hospital Rotterdam approved the study and all patients provided written informed consent before the procedure.

Results

Baseline clinical and procedural characteristics are described in Tables 1 and 2. Table 3 describes quantitative coronary angiography data pre- and post-intervention and at the 6-month follow-up.

In-stent radioactive segment

Neointimal hyperplasia measured within the margins of the stent is presented in Fig. 2. Intra-stent neointimal hyperplasia was significantly decreased in the radioactive mid-segment of the stent: 3·72 ± 3·3 mm^3 (8·6%), compared with the proximal: 7·90 ± 7·2 mm^3 (19·0%) and distal: 11·42 ± 10·5 mm^3 (25·6%) in-stent segments. Over the entire stent length there was a 30·48 mm^3 (14%) increase in neointimal hyperplasia. No evidence of remodelling was seen behind the stent with the total vessel volume remaining unchanged.

Table 1 Clinical characteristics

Age (mean)	52 (41–78)
Male (%)	69
Prior MI (%)	75
Unstable angina (%)	40
Smoking (%)	56
Hypercholesterolaemia (%)	69
Family history (%)	56
Hypertension (%)	40
Diabetes (%)	0

Table 2 Procedural characteristics

Vessel	
LAD	6
LCx	7
RCA	3
Lesion length (mm)	11·2 ± 4·5
Balloon length-post (mm)	15·6 ± 5·7
Final balloon size (mm)	3·9 ± 0·5
Max inflation pressure[1] (atms)	10 ± 4·0
Max inflation pressure[2] (atms)	16 ± 2·2
Balloon-to-artery ratio	1·12

Max inflation pressure[1]=balloon at time of stent implantation.
Max inflation pressure[2]=balloon inflation within stent.
LAD=left anterior descending coronary artery; LCx=left circumflex artery; RCA=right coronary artery.

Table 3 Angiographic data

	Pre	Post	FU
MLD	0·98 ± 0·40	2·26 ± 0·40	1·67 ± 0·48
DS	67 ± 14	26 ± 8	42 ± 13
RD	2·97 ± 0·46	3·06 ± 0·41	2·82 ± 0·43
Acute gain		1·28 ± 0·46	
Late loss			0·59 ± 0·49
Late loss index			0·57 ± 0·56

FU=6-month follow-up.
MLD=minimum lumen diameter; DS=diameter stenosis; RD=reference diameter.

In-stent non-radioactive segment

Significant neointimal in-growth was noted distally and proximally from 2–3 mm within the radioactive segment and extended on average to the extremities (non-radioactive) of the stent (see Fig. 3). Four individuals experienced angiographic restenosis in the proximal

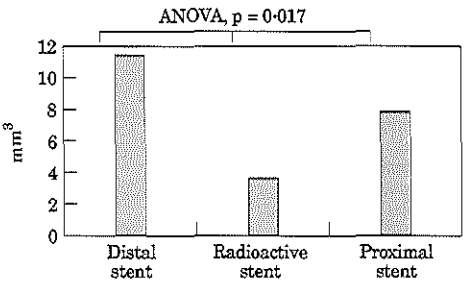

Figure 2 **Neointimal hyperplasia (mm^3) in the three in-stent segments. Each segment is standardized to a 5 mm length for comparison.**

portion of the stent. However, the greatest mean volume of tissue growth as quantified by intravascular ultrasound was seen in the distal stent. Neointimal hyperplasia, with a >50% stented cross-sectional area, was seen in eight patients. This was witnessed proximally (n=2), distally (n=2) and in both segments (n=4). Tissue growth in-stent was due to a combination of conventional neointimal hyperplasia and echolucent, hypodense material, described by this group as the 'black hole' (P. W. Serruys, personal communication, Rotterdam, 1999). This was witnessed (Fig. 4) in the non-radioactive proximal and distal in-stent segments in six out of the eight patients.

Total vessel volumes

No significant change in total vessel volumes or plaque behind the stent was seen between post-procedure and follow-up. No echolucent tissue was seen behind the stent.

Stent edge

Late lumen loss was seen at the stent edge without evidence of restenosis. On average, there was evidence of a decrease in total vessel volume, with little change in plaque as a cause of late lumen loss.

Stent activity

Mean stent activity at implantation was 6·9 ± 1·9 μCi.

Discussion

Dose-finding studies in humans have shown that in-stent neointimal hyperplasia is decreased in a dose-dependent manner after the implantation of stents with activity levels >3·0 μCi[3,4]. Unfortunately, stent edge restenosis was a side effect of this treatment modality at these activity levels. Because the stent edge is systematically

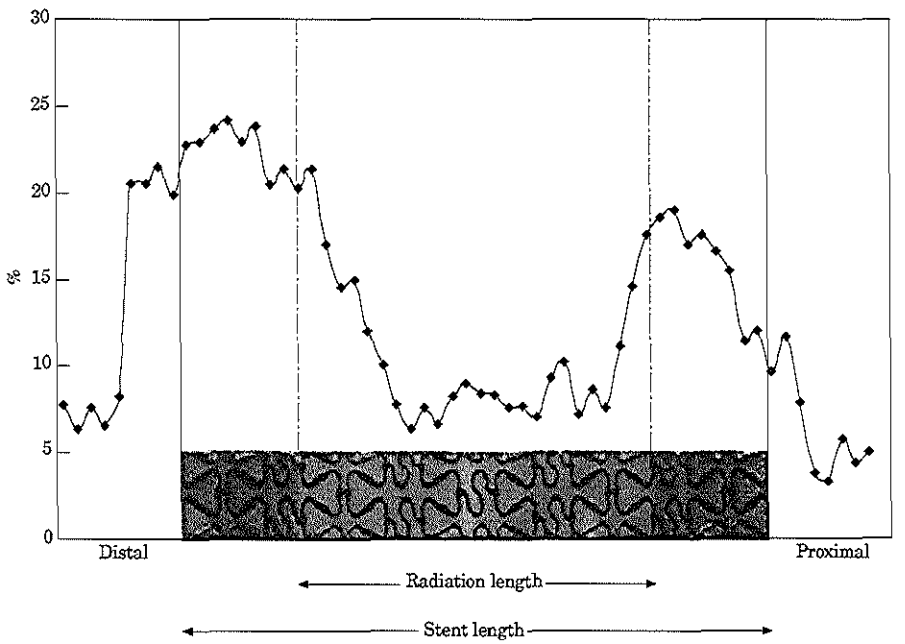

Figure 3 **Graph showing neointimal hyperplasia (% increase) over the length of the stent and edges. Note significant hyperplasia proximally and distally in-stent and the relative sparing of the radioactive mid-segment of the stent. Note also that significant in-growth begins within the radioactive segment of the stent and extends to the non-radioactive proximal and distal extremities of the stent.**

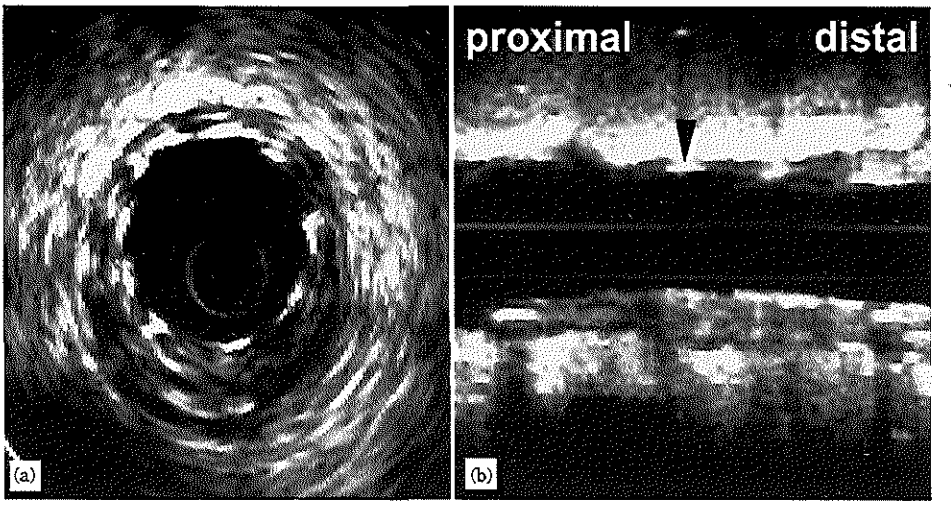

Figure 4 **Representative example of echolucent tissue ('black hole'). (a) A transverse section. A black hole is seen from 9 o'clock to 3 o'clock. (b) A longitudinal reconstruction. Arrowhead points to semi-circular echolucent tissue seen adjacent to the stent struts.**

damaged by barotrauma at the time of balloon expansion, a situation of geographical miss[11], in which the damaged edges receive low dose radiation, is germane to radioactive stenting in the absence of appropriately shaped balloons. Previously we have argued: 'If the candy wrapper (bilateral edge restenosis) were purely the result of negative remodeling induced by low-dose radiation in an injured area, then the lengthening of the stent by a non-radioactive, cold-end would be a logical solution to prevent remodeling at the extremities. If plaque constitutes a large percentage of the healing process manifested by the candy wrapper then cold-end stent implantation is unlikely to work. Similarly neointimal proliferation may occur at the edges of the radiation within stent using this treatment modality'[12]. This prediction appears to have materialized in the current study, with migration of the restenotic edge from outside the stent to within the stent at the edges of radiation.

Neointimal hyperplasia

Neointimal hyperplasia in the true radioactive segment was suppressed at the 6-month follow-up to a degree similar to that noted in the ^{32}P radioactive stent dose-finding trial previously reported by this group (mean neointimal hyperplasia=17·67 mm^3 (13·94%)), using a 15 mm stent[5]. Regrowth of tissue starting 1–2 mm within the radioactive extremes and extending out of the stent was noted in the ^{32}P radioactive stent dose finding trial, translating to significant stent-edge hyperplasia proximally. In the cold-end stent, neointimal hyperplasia was noted in the final millimetres of radiation and extended bilaterally. In the latter study, this left the true stent edges relatively, although not completely, spared as there remained evidence of tissue growth in three individuals, which started within the radioactive portion and continued to the true vessel lumen. No angiographic restenosis occurred in these three however. Again, we must assume that the position of such restenosis is caused by geographical miss. Why some individuals are affected and others not is unclear, but may be explained by an idiosyncratic individual response to healing, dose heterogeneity along the length of the stent, tissue type behind the stent, plaque burden and even strut apposition to the vessel wall.

Echolucent tissue

In nearly 50% of subjects, echolucent tissue was present within the stent at the distal or proximal (in-stent) edge of radiation and consituted on average 50% of neointimal ingrowth in areas of restenosis. These echolucent lesions had the following characteristics: a homogeneous black appearance without backscatter. Images with ring-down or other artefacts were excluded and no attenuation behind intraluminal echodense structures was seen. Exclusion of other causes of relative echolucency such as contrast[13], thrombus[14] or a lipid lake[15] was performed. Lesions were discrete and readily distinguishable from conventional neointimal hyperplasia. After radioactive stenting, all appeared to be juxtaposed to stent struts.

We have performed atherectomy on four such lesions detected at the 6-month follow-up after radioactive stenting and found that they contain a hypocellular matrix with areas of proteoglycan, similar to that seen in the animal model[16,17]. The mixture of neointimal hyperplasia and proteoglycan, which has a high water content, may explain the echolucent tissue adjacent to the stent struts noted in Fig. 5. Further pathological

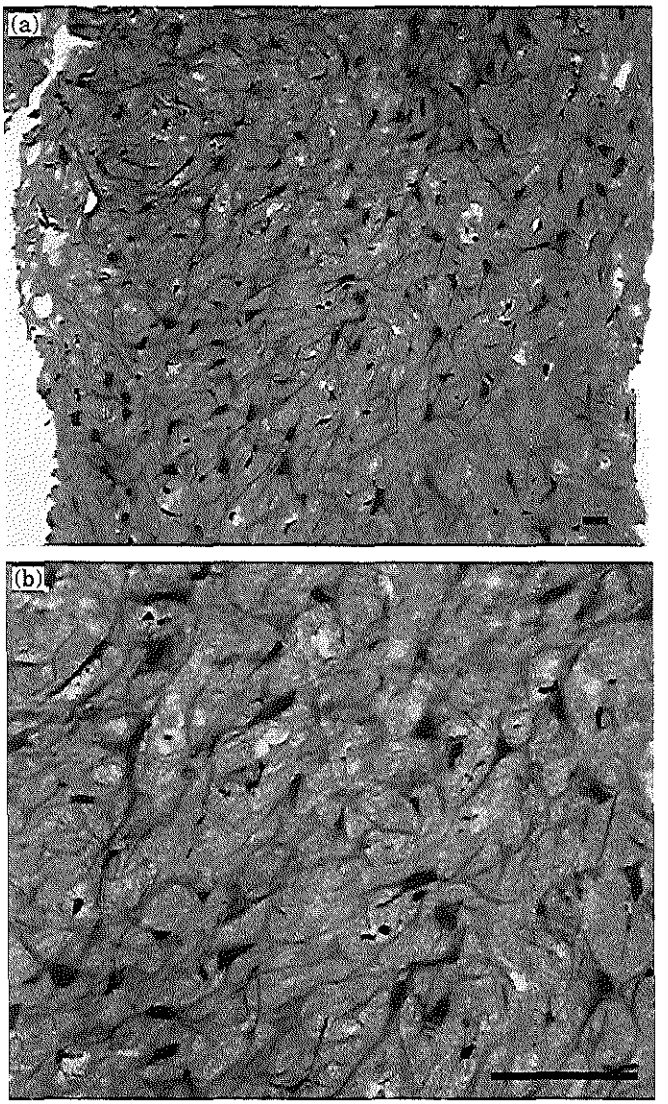

Figure 5 **Photomicrographs (a) and (b) show neointima consisting of arboryzing smooth muscle cells in a proteoglycan matrix. H&E stain; bars=50 μm.**

assessment is required before definitive comment can be made on this interesting observation. Equally, the long-term incidence of restenosis from such lesions is yet to be determined.

Edge remodelling

This was similar to that seen after non-radioactive stenting, whereby non-restenotic late lumen loss was due to negative remodelling[5,18].

Implications for the future: dealing with the edge effect

If the edge effect is the result of balloon-induced trauma and low dose radiation then limiting the trauma to outside the stent and expanding the irradiated area beyond the injured area should be attempted. For radioactive stents, conceivably the most practical approach may be to extend the area of irradiation beyond the injured area using a 'hot-end stent'. This involves literally concentrating the greatest activity of the stent at

the stent edges; such stents are already undergoing multicentre trials. A further therapeutic option is that of hybrid treatment with radioactive stent implantation followed by catheter-based therapy localized to the stent edges only.

Conclusion

Cold-end stent implantation, a strategy devised to prevent edge restenosis after radioactive stenting results in migration of the restenotic edge from outside the stent to within the stent at the edges of radiation. This adds credence to the hypothesis that injury and low-dose radiation stimulate neointimal hyperplasia[19].

The Wenckebach award was made to P. W. Serruys by the Dutch Heart Foundation and is utilized for brachytherapy research in the catheterization laboratory. I. P. Kay is supported by the National Heart Foundation of New Zealand, Auckland and the Ian Gordon Mackenzie Scholarship, University of Otago, Dunedin, New Zealand.

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Chapter 7

The black hole: echo-lucent tissue observed following intracoronary radiation.

Submitted

The black hole: echo-lucent tissue observed following intracoronary radiation

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ABSTRACT

Background Recent trials in humans have given us insight into some of the consequences of intracoronary radiation. We describe a new observation noted on intravascular ultrasound (IVUS): that of intraluminal echo-lucent tissue, dubbed the 'black hole', noted at 6-month follow-up.

Methods and Results We analyzed 128 consecutive patients enrolled in brachytherapy protocols. The control group (C) consisted of individuals who underwent PTCA with (n = 48) and without (n = 22) stent implantation. Radiation groups included those who underwent low activity (LA) (n = 18), high activity (HA) (n = 26) and cold – end (CE) (n = 18) radioactive stenting. The Novoste Betacath (n = 39) and Guidant (n = 27) catheter-based radiation systems were also employed. At 6 – month follow – up echo-lucent tissue was identified in a total of 28 cases (22%). Angiographic restenosis occurred in 17 cases (61%). Of those lesions with restenosis echo-lucent tissue comprised 50% of the neo-intimal hyperplasia. No echo-lucent tissue was seen in the control group or in the LA group. HA and CE radioactive stents were most commonly associated with echo-lucent tissue (incidence 35% and 39% respectively). All occurred at the proximal or distal edges of radiation. Echo-lucent tissue was seen in all groups treated with catheter-based radiation with and without stenting. Atherectomy was performed on 4 lesions. Pathology demonstrated smooth muscle cells scattered in extracellular matrix containing abundant proteoglycans and an absence of elastin and mature collagen.

Conclusions This paper is the first to describe atherectomy samples extracted from humans after radioactive stent implantation. Also it is the first to link the IVUS finding of echolucency noted after intracoronary radiation with tissue rich in proteoglycans while poor in mature collagen and elastin.

Intracoronary radiation, a therapeutic modality aimed at decreasing restenosis, has been investigated in both animals and humans for several years. With the advent of human trials we have started to understand the consequences of this treatment. These include non - healing dissection[1], late occlusion[2] and positive remodeling[3]. We describe a further new finding: an echo-lucent area within the lumen of the coronary artery, noted using intravascular ultrasound (IVUS). This phenomenon has been dubbed the 'black hole'. We describe the finding in terms of IVUS characteristics and present data on its incidence in various subgroups treated conventionally and with radiation. Finally we describe the pathological findings of this entity.

METHODS

We analyzed 128 consecutive patients enrolled in brachytherapy protocols, who had completed 6 - month follow-up that included angiography with IVUS. These protocols included individuals who had undergone catheter – based radiation using the ^{90}Sr / ^{90}Y Betacath™ (Novoste, Norcross, Ga) and ^{32}P Guidant (Santa Clara, CA) systems. The radioactive stent group comprised those who received 0.75 – 1.5μCi (n = 18), 6.0 – 12.0μCi (n = 26) and 'cold – end' (n = 18) stents (Isostent™ Inc., San Carlos, CA, USA). The control group included individuals who underwent PTCA with (n=48) and without stent implantation (n=22).

Catheter – based radiation

The Novoste Betacath and the ^{32}P Guidant β-radiation systems have been described in detail elsewhere [3,4]. We followed certain steps to ensure the correct identification and analysis of the irradiated segment post intervention and at 6 – month follow - up. First, an angiogram was performed after positioning the delivery catheter and the relationship between anatomical landmarks and the two gold markers were noted. Typically, the aorto-ostial junction and the side branches were used as landmarks. The landmark closest to either of the gold markers was used as a guide. During the motorized IVUS pullback, all side branches were counted and the guiding landmark was identified. The correct selection of the marker was confirmed by visualizing the position of the IVUS probe during a contrast injection. At follow-up, we selected the same region of interest and compared it with that after treatment.

Radioactive stent

The properties of low (0.75 – 1.5μCi) and higher activity (6.0 – 12.0μCi) radioactive stents and procedural characteristics specific to their implantation have been described elsewhere[5]. All stents were implanted with a stent to artery ratio of 1.1:1. 'Cold - end' stents were 27.3mm in length and available in diameters of 3.0 & 3.5 mm. The distal and proximal 5.7mm of the stent was non-radioactive, whereas the central 15.9mm had an activity of 3.0-24.0 μCi (see Figure 1).

IVUS Acquisition

We used a mechanical 30MHz IVUS system (ClearView, CVIS, Sunnyvale, CA). Motorized pullback was performed at 0.5mm/sec. We examined the entire segment subjected to radiation, plus the associated 10mm proximal and distal edges. For radioactive stents this included 10mm proximal and distal to the final stent strut. Images were stored on S-VHS tape for later analysis. Findings were verified by 3 independent observers, who were blinded to whether images were from control or radiation cases.

IVUS definition of echo-lucent tissue

Lesions with the echo-lucent tissue had the following characteristics: a homogeneous black appearance without backscatter. Images with ring-down or other artefacts were excluded as were intraluminal echodense structures with associated attenuation. Exclusion of other causes of relative echolucency such as contrast[6], thrombus[7] or a lipid lake[8] was performed. Lesions were discrete and readily distinguishable from conventional neointimal hyperplasia (Fig. 2, 3). After radioactive stenting all lesions were observed adjacent to stent struts.

Definitions

The following dimensions were measured in each group: total vessel area (TVA), lumen area (LA), the area of echo-lucent tissue and the percentage of neointimal hyperplasia (NIH) caused by the echo-lucent tissue in the cross-section of greatest stenosis. Restenosis at 6–month follow-up was defined using standard angiographic criteria after off-line quantitative coronary angiography (diameter stenosis > 50%).

Medication

All patients received clopidogrel for between 1 month (conventional stenting) and 3-6 months (stenting plus catheter – based radiation or radioactive stenting), plus life-long aspirin.

Immunohistochemistry

For immunostaining, sections were preincubated with 0.3% hydrogen peroxide and Protein Block Serum-Free (X0909, Dako Corp, CA). A mouse monoclonal antibody against α-smooth muscle actin (1:5000 dilution, Dako) was used to identify smooth muscle cells. Polyclonal antibodies against biglycan (LF-51) and decorin (LF-122) were used for identification of proteoglycans (antibodies kindly provided as a gift from Larry Fisher, NIH, Bethesda, Maryland). Before incubating with proteoglycan antibodies, sections were first incubated with 1U/L chrondroitinase ABC (code #100332, Seikagaku Corp., Tokyo, Japan) for 15 minutes at 37°C to detach glycosaminoglycan side chains from the protein core; this procedure intensifies staining[9]. All primary antibodies were incubated overnight in a humidified chamber at 4°C. After rinsing in PBS, the primary antibody was labeled by a biotinylated link antibody directed against mouse using a peroxidase based LSAB kit (Dako). Positive staining (brown reaction product) was visualized

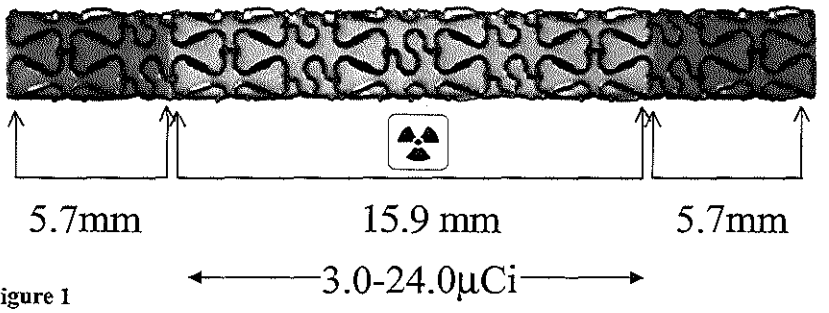

Figure 1
Cold-end stent with central radioactive segment and proximal and distal non-radioactive segments

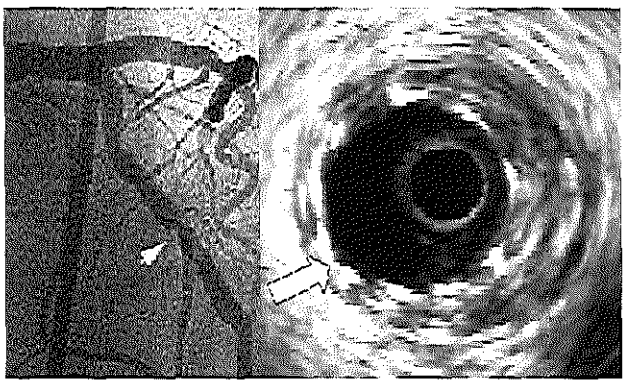

Figure 2
Left coronary angiogram performed at 6-month follow-up. Proximal in-stent restenosis is seen in a 6-12μCi stent implanted in the circumflex artery (left frame).
IVUS performed at 6 month follow-up demonstrating homogeneous black tissue from 6 to 1 o'clock (right frame).

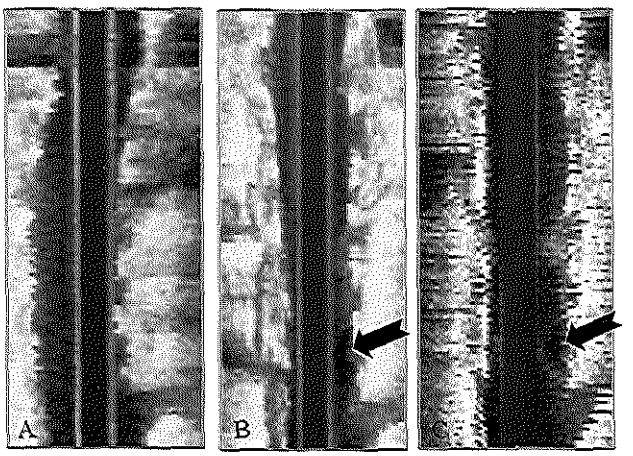

Figure 3
a. Baseline longitudinal IVUS reconstruction of freshly implanted stent.
b. Longitudinal reconstruction of the same transverse IVUS image seen in Fig 2. This confirms the presence of a uniform black semi-circular structure with a thin cap.
c. The same image seen at 1 year, with echo-lucent tissue in a similar position as verified by the vascular structures seen at 2, 5 and 8 o'clock. Note the greater reflectivity of the echo-lucent tissue and the thicker fibrous cap present.

with a diaminobenzidine (Dako). After immunostaining, the sections were counterstained with Gill's hematoxylin, dehydrated in a graded series of alcohols, rinsed in xylene and mounted in Permount (Fisher Scientific).

RESULTS

At 6 – month follow - up 28 discrete areas of echo-lucent tissue ('black hole') (22%) were identified. No echo-lucent tissue was seen in the control group or in the low activity radioactive stent group. Angiographic restenosis was present in 61% of cases where echo-lucent tissue was present. Of those lesions with restenosis, echo-lucent tissue was on average responsible for 50% of neointimal hyperplasia. More severe stenosis was more frequently observed in the 6.0-12.0μCi and cold-end radioactive stent groups (mean stenosis = 63.1% ± 24.1) compared with catheter-based techniques (mean stenosis = 37.2% ± 20.5), p=0.005. Mean length of the echo-lucent tissue was 4.0mm ± 1.6mm (range 2-8mm).

Radioactive stent

Higher activity and cold-end radioactive stents were most commonly associated with echo-lucent tissue (Table 1). All occurred at the proximal and distal margins of radiation within the stent or at the stent edges. By definition this fall-off in radiation occurred in the final 1-2mm of 6.0-12.0μCi stents and in-stent for cold-end stents. Bilateral echo-lucent tissue was seen in 5 out of 7 cases that presented with restenosis 6 months after cold-end stent implantation. In four of theses cases the proximal edge was more severely affected.

Catheter-based

Echo-lucent tissue was seen in all groups treated with catheter-based radiation with and without stenting. These tended to be smaller lesions than those seen in the radioactive stent group (Table 1). After catheter-based radiation only one of the echo-lucent tissues described involved geographical miss (area of injury associated with a fall-off in radiation)[10].

Pathology features

Atherectomy was performed on 4 individuals (AtheroCath - Bantam™, DVI, Guidant, Temecula, CA, USA). Macroscopic assessment of the tissue samples showed two types of tissue: dark yellow, often containing pieces of stent strut and white more fibrotic appearing tissue (Fig. 4A). Microscopy revealed tissue containing smooth muscle cells in abundant extracellular matrix (myxoid change) with two distinct regions (Fig.4B, C) and containing abundant proteo-glycans (Fig.4D). Region 1 (Fig 4E) was more cellular in nature, contained collagen and elastin (Fig 4C), and was not distinguishable from normal restenotic tissue. Region 2 (Fig 4F) was more sparsely populated showing pyknotic nuclei, with some of the extracellular matrix having a coagulated or dense appearance (fibrinoid change). The latter was thought to be tissue constituting the echo-lucent tissue.

The area of the myxoid, proteoglycan rich matrix was thought to constitute the black hole. Three of the four biopsies were stained for a-actin (Fig 5A) to confirm presence of smooth muscle cells and for biglycan (Fig 5B), which is the dominant proteoglycan in restenotic lesions[9]. All three biopsies were strongly postive for biglycan and one biopsy stained for decorin was weakly positive.

DISCUSSION

Echo-lucent tissue ('black hole') noted at 6 – month follow-up was uniquely associated with intracoronary radiation. More common after radioactive stent (>6.0μCi) implantation, it was frequently located adjacent to the stent struts in areas of radiation fall-off, where it was associated with greater restenosis than the catheter-based techniques.

Echo-lucent tissue may be a dominant cause of restenosis as seen in 4 patients (1,2,5 and 10). Overall it appeared to contribute to approximately 50% of the restenotic burden associated with NIH seen at 6-month follow-up. The lesion may be missed on IVUS examination due to its echolucency, caused by tissue rich in proteoglycans and poor in mature collagen and elastin.

What is unclear is the cause of such lesions. Certainly irradiation is associated with proteoglycan accumulation in various tissues[11,12]. Hehrlein has noted that the increase in neointimal volume in arteries treated with external beam radiation (EBR) was predominantly due to enhanced extracellular matrix production. This study suggested that the accumulation of extracellular matrix after stent deployment was augmented by external beam radiation and that excessive matrix formation was a determinant of failure of radiation therapy to prevent restenosis. The atherectomy samples of the current paper reflect changes seen in Carter's porcine model[12] with radioactive stents (Fig 2G & H). Carter has reported myxoid changes in low, intermediate and high activity stents (30%, 60% and 37% respectively) while no myxoid change was seen in control stents (personal communication, 2000). This would indicate that the echo-lucent tissue is a general response to irradiation of damaged vascular tissue.

The matrix seen is rich in biglycan proteoglycan; biglycan secretion by smooth muscle cells in culture has been shown to be controlled by TGF-β[13,14]. Therefore it is likely that radiation may induce greater TGF-β production that results in excessive biglycan production and formation of echo-lucent tissue on IVUS.

O'Brien[15] and colleagues suggest that biglycan may bind apoE and apoB in atherosclerotic intima. They also raise the possibility that apoE may act as a bridging molecule that traps apoA-I-containing HDL in atherosclerotic intima. Taken together these findings are consistent with the hypothesis that biglycan may contribute to the pathogenesis of atherosclerosis by trapping lipoproteins in the artery wall.

Atherectomy samples taken at points

	Location	% BHA of NIH	Restenosis (QCA)
Radioactive stent			
6-12 μCi (n=26)			
1	P edge	96	Y
2	P edge	100	Y
3	D edge	56	N
4	P edge	64	Y
5	P edge	100	Y
6	P edge	48	Y
7	D edge	71	Y
8	P edge	52	N
9	D edge	68	N
Cold-End (n=18)			
10	P In stent*	100	Y
11	D In stent*	42	N
12	P In stent*	50	N
13	D In stent*	26	Y
14	P In stent*	48	Y
15	D In stent*	38	N
16	P In stent*	51	Y
Guidant CBS (n=16)			
17	In-stent	26	Y
18	In-stent	34	N
19	Out of stent	45	Y
Betacath CBS (n=18)			
20	In stent	48	N
21	In-stent	26	Y
22	In-stent	26	N
23	In-stent	56	N
Guidant: no stent (n=11)		%BHA of NIH	Restenosis
24		34	Y
25		90	N
Betacath: no stent (n=21)			
26		27	Y
27		16	Y
28		18	Y

CBS=catheter-based radiation plus stenting. P=proximal. D=distal. * at junction of radioactive and non radioactive segment of the stent. NIH=neointimal hyperplasia.

%BHA of NIH = % of NIH caused by echo-lucent tissue.

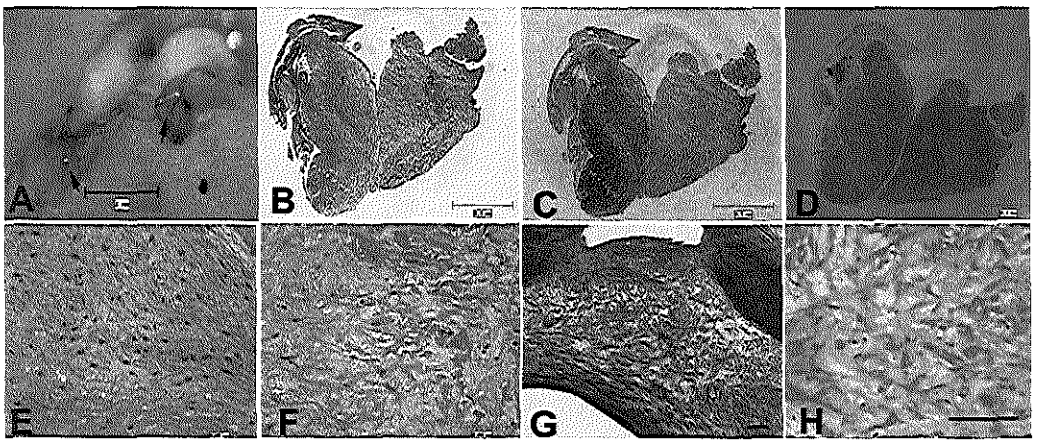

Figure 4

Fig. 4A Gross macroscopy of atherectomy specimen, showing that darker more yellow tissue overlies stent strut remnants (arrow), with a cover that is white in appearance.

Fig. 4B. Hematoxylin-Eosin stain showing two distinct regions; region 1 being more cellular than region 2.

Fig. 4C. Elastin stain, showing that region 1 consists of a more elastin and collagen rich tissue as compared to region 2.

Fig. 4D. Alcian Blue stain showing that the extracellular matrix contains large amounts of proteoglycans, most of which is hyaluronic acid (differential stain, not shown).

Fig. 4E. Detail of region 1, showing tissue that is similar in appearance to normal restenotic tissue.

Fig. 4F. Detail of region 2, showing sparse and pyknotic cells.

Fig 4G (Movat stain) and Fig 4H (H&E). Porcine model with 3μCi stent at 6 months. Extensive NIH consisting of SMCs in a proteoglycan matrix.

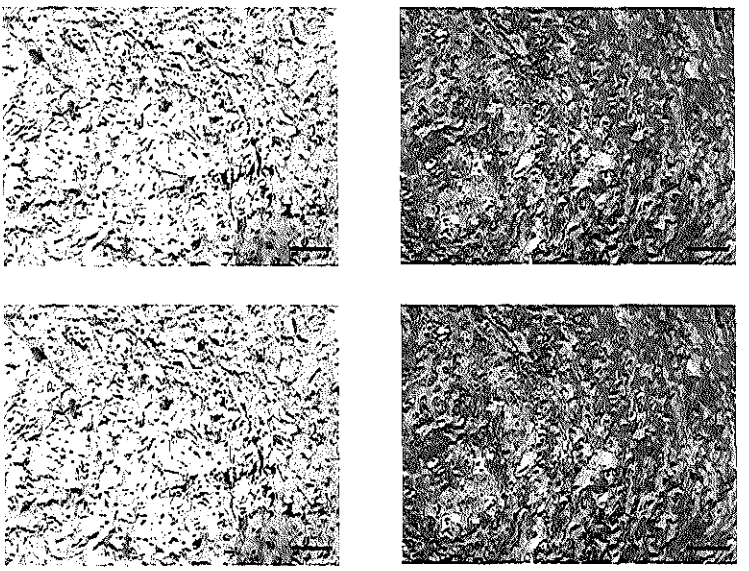

Figure 5

Fig 5A. Immunoperoxidase stained section showing a-actin positive smooth muscle cells.

Fig 5B. Immunoperoxidase stained section showing strong matrix positivity for biglycan.

where echo-lucent tissue is seen on IVUS shows aberrant nuclear morphology, suggesting ongoing cell death. This process continues to take place long after stent radioactivity has decreased to background levels. This indicates that radiation indeed has long-term effects. The presence of fibrinoid change may also be indicative of delayed healing, as was also seen in Carter's report.
With time the echo-lucent tissue becomes more discernible on IVUS due to its echodense cap (Figure 3). This cap is also seen on pathology showing collagen and elastin - rich tissue. This may be in keeping with a phenotypic change in the SMCs, allowing them to produce collagen and elastin - rich matrix typical of mature NIH with a lack of proteoglycan.

Conclusion

This paper is the first to describe atherectomy samples extracted from humans after radioactive stent implantation. Also it is the first to link the IVUS finding of echolucency noted after intracoronary radiation in various modalities with tissue rich in proteoglycans while poor in mature collagen and elastin

Limitations

Atherectomy was only performed in 4 patients and the findings described here will need to be substantiated with greater numbers. The issue of radioaction dosimetry is complex and fundamental, however is beyond the scope of this report.

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Part 4

Attempts to prevent edge restenosis.

Chapter 8

Angiographic follow-up after ^{32}P β-emitting radioactive "Cold Ends" Isostent implantation. Results from Aalst, Milan and Rotterdam.

Submitted

Angiographic follow-up after ^{32}P β-emitting radioactive "Cold Ends" Isostent implantation. Results from Aalst, Milan and Rotterdam.

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ABSTRACT

Aims. ^{32}P β-emitting stents with an activity of 3-24 μCi have shown >40% edge restenosis due to neointimal hyperplasia and vessel remodeling. The aim of this trial was to evaluate whether extending the radioactive stent with non-radioactive Cold Ends might diminish this edge restenosis by preventing remodeling at the injured extremities.

Methods and results. The 25 mm in length (15 mm radioactive center segment & 5 mm non-radioactive ends) "Cold Ends" Isostents had an activity of 6-24 μCi at implantation. When possible, direct stenting was performed. A total of 43 stents were implanted in 43 pts with de novo native coronary artery disease. Treated vessels were LAD (n=20), RCA (n=15) and LCx (n=8). QCA measurements were done pre-, post-procedure and at 6-mo FU. There were 2 procedural & 1 subacute stent thrombosis. One late (3.5 months) stent thrombosis occurred after discontinuation of antiplatelett therapy. QCA results are available for 37 pts. Eight in-stent restenoses were located in the non-radioactive (Cold Ends) segments, and 5 restenoses were both at the radioactive segment and at a Cold End.

Conclusion. Restenosis of the radioactive segment occurred in 15%, all occurring at the transition zone from radioactive to non-radioactive. The overall in-stent restenosis rate was 22%. Cold Ends stents therefore have a relatively low restenosis rate compared to other radioactive stents. Edge restenosis is mainly caused by a proliferative response, induced by a combination of low dose radiation and balloon injury.

Key words β-particles • angioplasty • radioisotope • restenosis • stent

INTRODUCTION

Vascular brachytherapy with a radioactive source after PTCA or stent implantation has been shown, in several clinical trials, to inhibit the process of neointimal hyperplasia and thereby in-stent restenosis [1-4]. Several animal trials have demonstrated a dose-related reduction of in-stent restenosis, following radioactive stent implantation [5-7]. However, a dose-dependent delay in endothelialization of the stent was shown, thereby increasing the risk of subacute and late thrombotic occlusions [6,8].

In patients treated with implantation of ^{32}P radioactive stents with activities ranging from 0.75 to 12 μCi, angiographic restenosis was reported in 43-62% of the cases with the restenosis being primarily located at the edges of the stent and caused by neointimal hyperplasia and/or vessel remodeling.[9]. These edges represent an area where tissue is subjected both to balloon-induced trauma and a lower dose of radiation, which may stimulate edge restenosis [7,10]. The aim of this trial was to evaluate whether extending the radioactive stent with non-radioactive Cold Ends might diminish this edge restenosis by preventing remodeling at the injured extremities.

METHODS

Patient Population

The ^{32}P radioactive "Cold Ends" stent trial was a non-randomized multi-center trial to evaluate the safety and efficacy of radioactive "Cold Ends" stent implantation, with activities ranging from 6-24 μCi. The data presented here represents all patients treated with "Cold Ends" stents, and were treated at the centers in Aalst, Milan, and Rotterdam.

Patients with single, de novo, native, coronary lesions, with a maximum lesion length of 15 mm (treated with a 25 mm Cold Ends stent), and objective evidence of ischemia were eligible. Exclusion criteria were: recent MI (CK-MB > 3 times the upper limit of normal, within 5 days of the intervention); left ventricular ejection fraction <40%; allergy or contraindication to aspirin, ticlopidine, clopidogrel or nickel; lesions located in the left main coronary artery.

The Medical Ethical Committees of the enrolling centers approved the study. All patients provided written informed consent before the procedure. The trial was conducted according to the GCP guidelines.

Radioactive stent, dosimetry and safety issues

The BXT™ Betastent (Isostent™ Inc., San Carlos, CA, USA) was investigated in this trial. It was 25 mm in length and available in diameters of 3.0 & 3.5 mm. The 15 mm center segment was made radioactive by Phosphorus-32, whereas both 5 mm edges (the Cold Ends) were kept non-radioactive [7]. The initial activity of the stents was measured and thereafter the date at which the radioactivity had decreased to 6-24 μCi (radioactivity level suitable for implantation) was calculated. All personnel were trained in

the appropriate handling of radioactive materials. During implantation the lucite shield enclosing the stent and the sheathed introduction system prevented exposure of the operator to the radiation of the stent. All disposable materials, which were in contact with the stent, were immediately disposed of in a plexiglas container.

Quantitative coronary angiography

Quantitative coronary angiography (QCA) was performed pre-procedure, post-procedure, and at 6-month follow-up. Coronary angiography was performed after intracoronary administration of nitrates. The off-line analysis of at least two orthogonal projections was performed by means of the CAAS II analysis system (Pie Medical B.V., Maastricht, The Netherlands) by the Thoraxcenter Rotterdam angiographic corelab. Calibration of the system was based on dimensions of the catheters not filled with contrast medium [11-13]. Lesion length was measured by means of a computer algorithm [13]. Procedural success was defined as %DS <30%, measured by on-line QCA. Acute gain was defined as MLD post-procedure minus MLD pre-procedure. Late loss was defined as MLD post-procedure minus MLD at follow-up. Late loss index was defined as late loss divided by acute gain [14]. For analytical purposes, 3 regions of interest were defined: 1) target vessel, 2) target lesion (total stent) and 3) radioactive area. The radioactive area was defined as the segment, which included only the radioactive segment of the stent, 15 mm in length. The target lesion was defined as the total stent area, consisting of the radioactive segment and both Cold Ends, being 25 mm in length. The target vessel was defined as the target lesion and the remaining segments of the treated vessel.

QCA Methodology

First, the minimum lumen diameter (MLD), reference diameter (RD) and diameter stenosis (DS) were measured from side-branch to side-branch for the target vessel. Subsequently, the MLD, mean diameter (MD) and DS were measured for the total stent (approximately 25 mm in length). Finally, the MLD, MD and DS were measured for the radioactive segment (approximately 15 mm in length), First the total stent (approximately 25 mm in length) was delineated as the region of interest, by means of a proximal and distal cursor. Thereafter, by moving the cursors 1/5 of the total stent length (approximately 5 mm) away from the proximal and distal stent edges towards the center of the stent, the radioactive segment (approximately 15 mm) was identified. Target lesion restenosis was defined as >50% DS at follow up, located within the target lesion. Cold Ends restenosis was defined as >50% DS at follow up, located at the proximal and/or distal Cold Ends segment of the stent.

Procedure and follow-up

Patients received 250 mg aspirin and 10000 international units heparin at the initiation of the procedure. The

ACT was maintained at >300 seconds. Preferably direct stenting was performed. The radioactive stent was implanted at a nominal deployment pressure of 8-18 atmospheres. Also, post-dilatation was avoided to minimize balloon trauma. The radioactive segment of the stent had to completely cover the original lesion length. Extreme care was taken to minimize trauma at both edges by taking the following, previously published [10], precautions: The best angiographic view to optimize stent visualization was chosen and the diaphragm was used to further enhance stent imaging. If needed, stent deployment was optimized using shorter post-dilatation balloons of larger diameter, to higher pressures. All post-dilatation balloons had 1 radio-opaque marker at both extremities. (see Table 1 for balloon inflation and stent deployment data). All patients received either ticlopidine 250 mg BID or clopidogrel 75 mg daily for 6-7 months after stent implantation and aspirin ≥80 mg daily indefinitely. CK and CK-MB measurements were made and the ECG was recorded at 6 and 12-18 hours post procedure in all patients.

Patients returned for 1 and 6-month clinical follow-up. An ECG was recorded at each visit. Clinical endpoints were: death, Q-wave MI (using the Minnesota code criteria [15]), non Q-wave MI (CK-MB rise >2 times normal upper limit), target lesion revascularization (reintervention inside the stent area), target vessel revascularization (revascularization of any segment of the treated vessel), non-target vessel revascularization, subacute[16] and late[17] thrombotic occlusion of the target vessel.

At the 6-month visit an exercise stress test was performed. Revascularization was performed on the basis of clinical symptoms and/or objective evidence of ischemia.

Statistical analysis

Data is presented as mean ± standard deviation. Continuous data was compared by means of the two-tailed Student's t-test or linear regression when appropriate.

RESULTS

Baseline characteristics

Baseline demographics and anginal state are shown in Table 2, lesion characteristics in Table 3.

Procedural data

All 43 stents were successfully implanted in 43 patients. All patients were successfully treated with a single Cold Ends radioactive stent. Five patients received additional non-radioactive stents due to procedural dissections. There were 3 transient stent occlusions: 2 procedural & 1 subacute stent thrombosis. The last occurring during an IVUS evaluation of the stent performed 1 day post procedure for logistic reasons. None of these stent thrombosis lead to a myocardial infarction. All other procedures were uncomplicated. Procedural success was achieved in all, but 2, patients. These 2 patients had a DS of 33 and 30%.

Follow-up

All patients were angina free at hospital discharge. At 30-day follow-up no other subacute stent thrombosis occurred. Thirty-nine (91%) patients remained angina free, whereas 4 (9%) patients had recurrent AP. One late (3.5 months) stent thrombosis, without total occlusion, occurred after discontinuation of all antiplatelet therapy by the patient himself, leading to a non-Q-wave MI, for which a primary target lesion revascularization was performed. All 43 patients returned for 6-month clinical follow-up (see Table 4). Thirty-three (77%) were asymptomatic and 10 (23%) patients had Angina Pectoris Class: CCS 1 (n=1), CCS 2 (n=6), CCS 3 (n=1) and CCS 4 (n=2, including the above mentioned MI). Six-month angiographic follow-up was performed in 37 (86%) patients. The remaining 6 (14%) patients refused; 5 were asymptomatic and 1 had AP CCS 2. No additional late occlusions were observed during the 6-month follow-up. Eight (22%)

Table 1. Balloon inflation & stent deployment data, measured by quantitative coronary angiography.

	Predilatation	Stent Deployment	Postdilatation
Nom. Size Balloon, mm	2.68±0.51	3.21±0.37	3.48±0.56
Balloon Length, mm	18±4		20±5
Stent Length, mm		25±3	
Balloon Artery ratio	0.90:1		1.16:1
Stent Artery ratio		1.07:1	
Direct stenting		16 (37%)	
No post-dilatation			10 (23%)

patients had angiographic restenosis (see Table 5). Nine (21%) patients underwent a target lesion re-PTCA: 7 due to binary restenosis (DS >50%), 2 patients were treated for recurrent angina with a DS <50%: 1 patient had recurrent angina and an MLD of 1.71, while the other was the one with the late stent thrombosis, leading to an acute MI (see above), with an MLD of 1.69 mm. One restenotic patient was treated medically since this patient was both asymptomatic and had a negative stress test. There were 2 additional repeat PTCAs: 1 because of progression of atherosclerosis in the target vessel and 1 because of progression of atherosclerosis in a non-target vessel.

QCA measurements

QCA data are presented in Table 5. Location of the restenosis is summarized in Table 6. Stents implanted by direct stenting followed by post-dilatation or direct stenting without post-dilatation have a significantly worse late loss index at follow-up compared to stents implanted after balloon predilatation (see Figure 1). Cold Ends stents showed only in 1 patient (3%) a diffuse restenosis (both diffuse throughout the radioactive segment and proximal Cold End) restenosis, while other non-radioactive stents have the tendency to be more diffuse restenotic. For a patient example see Figure 2.

Radiation doses

Stent activity level was 7.58±2.78 μCi at implantation. There was no significant correlation between stent activity and late loss or late loss index at follow-up.

DISCUSSION

The results of this non-randomized study show that the implantation of a 6-24 μCi β-radioactive "Cold Ends" stent is safe and feasible, with a total MACE rate of 26% at 6-month follow-up.

This trial was conducted to investigate whether edge restenosis [9], occurring in more than 40% of the cases, treated with an isodose radioactive stent [18] and possibly caused by a combination of balloon injury (barotrauma) and lower radiation dose at the stent-edges [7,10], can be diminished by using Cold Ends radioactive stents. Using IVUS analysis, edge restenosis seemed to be caused both by negative remodeling and neointimal hyperplasia [19-21]. Therefore, it was hypothesized that edge restenosis could be reduced if the remodeling component of the edge restenosis phenomenon could be attenuated by the scaffolding properties of Cold Ends stents. The Cold Ends stents were manufactured as 15 mm isodose radioactive stents, extended with 5 mm non-radioactive Cold Ends segments. Furthermore, in order to control the extent of the barotrauma caused by predilatation outside the stent area, direct stenting was performed whenever possible. Also, post-dilatation of the stent was only performed, when necessary, and strictly inside the stent.

What was observed in this trial was a shift of the restenosis, usually occurring at the edges of the isodose radioactive stent, into the Cold Ends segment. More specifically, the most severe restenosis occurred at the transition zone from radioactive to non-radioactive segments,

Table 2. Baseline patient demographics and anginal status.

Gender	Male	34	(79%)
	Female	9	21%)
Age	Average	58	
	Range	41-80	
Risk Factors	Previous MI	20	(47%)
	Diabetes Mellitus	3	(7%)
	Hyperlipidemia	32	(74%)
	Hypertension	16	(37%)
	Smoking	16	(37%)
	Family History	19	(44%)
Anginal Pectoris	Stable	32	(74%)
	Unstable	11	(26%)

Table 3. Baseline lesion characteristics.

Treated vessel	LAD	20 (46.5%)
	LCx	8 (19%)
	RCA	15 (34.5%)
Lesion type	A	15 (35%)
	B	26 (60%)
	C	2 (5%)
Total occlusions		2 (5%)
Lesion length		10±4 mm

Table 4. Six-month clinical follow-up.

Angina Free	33 (77%)
Target Lesion Revascularization (TLR)	9 (21%)
PTCA	9 (21%)
CABG	0 (0%)
Target Vessel Revascularization (incl. TLR)	10 (23%)
Non Target Vessel Revascularization	1 (2%)
Late Occlusion	1 (2%)
Myocardial Infarction	1 (1%)
Death	0 (0%)
Total MACE	11 (26%)

Table 5. QCA Analysis (n=37).

	Pre	Post			Follow-up		
		Radioactive	*Total Stent*	*Vessel*	*Radioactive*	*Total Stent*	*Vessel*
MLD	1.03±0.44	2.68±0.46	2.57±0.43	2.14±0.44	2.04±0.53	1.79±0.56	1.66±0.49
%DS	66±13	10±12	13±13	28±11	28±17	37±19	42±16
RD or *MD*	2.99±0.60	*3.00±0.45*	*3.03±0.45*	3.00±0.52	*2.66±0.51*	*2.56±0.49*	2.87±0.51
Acute Gain		1.66±0.57	1.55±0.55	1.11±0.54			
Late Loss					0.65±0.57	0.79±0.58	0.49±0.49
LLI					0.42±0.41	0.60±0.64	0.55±0.83
Restenosis, n (%)					5 (14%)	8 (22%)8 (22%)	

*results of all 37 patients, who returned for angiographic follow-up, 6 patients refused.

%DS = % diameter stenosis, FU = follow-up, LLI = late loss index, MLD = minimum lumen diameter, MD = mean diameter, Pre = pre-procedure, Post = post-procedure, Radioactive = radioactive segment (15mm in length), RD = reference diameter, Total Stent = radioactive segment and both Cold Ends (25mm in length), Vessel = Total vessel (sidebranch to sidebranch). MLD, MD, RD., Acute Gain and Late Loss measurements are in mm.

Table 6. Location of the Restenosis (n=8).

Proximal Stent Segment	5 (14%)
Distal Stent Segment	1 (3%)
Prox. & Distal Stent Segment	2 (5%)

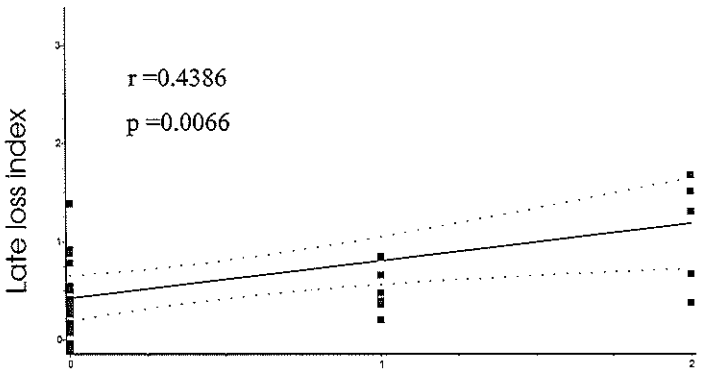

Figure 1.
Late loss index at follow-up versus direct stenting of the radioactive stent with and without postdilatation.
Stents implanted by direct stenting followed by post-dilatation or direct stenting without post-dilatation have a significantly worse late loss index at follow-up compared to stents implanted after balloon predilatation (p=0.0066). 0=predilatation followed by stenting, 1=direct stenting & post-dilatation, 2=direct stenting without post-dilatation.

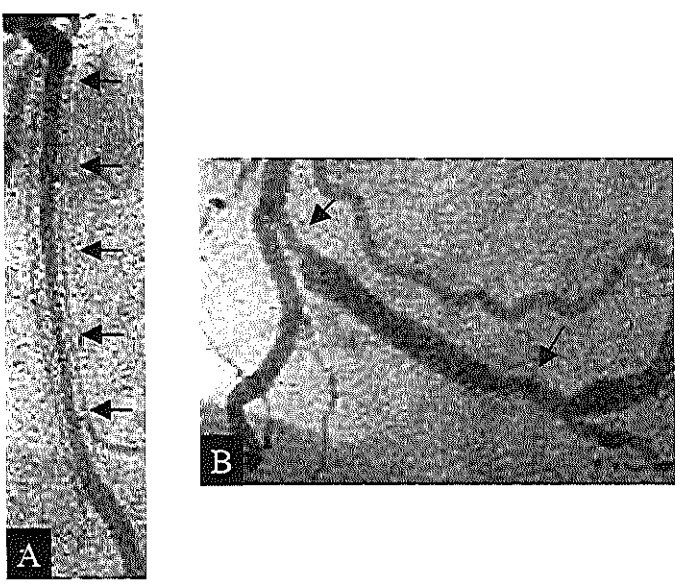

Figure 2.
Example of a patient at 6-month angiographic follow-up.
The Wallstent (4.5 long), implanted in the ramus circumflexus, had a diffuse in-stent restenosis (see arrows in Figure A), while the Cold Ends stent, implanted in the right coronary artery, showed a good result in the radioactive segment, with Cold Ends restenosis (see arrows in Figure B).

a region located in dose fall off. This phenomenon has also been recently demonstrated, by the group of the Thoraxcenter, in an experimental setup in which half radioactive/half non-radioactive stents were implanted in coronary arteries of pigs. It was clearly demonstrated that the peak level of neointimal hyperplasia was observed specifically in front of the last radioactive strut, thus in the region of dose fall-off. This strongly suggested that the combination of low dose radiation in association with chronic injury by the stent, implanted in non-atherosclerotic tissue, is the main determinant of neointimal hyperplasia [22]. Other trials also noted that low dose radiation had a stimulatory effect, compared to higher dose radiation [23-25]. All these trials give support to the hypothesis that a combination of low-dose radiation and balloon injury, actually stimulates neointimal hyperplasia. Edge restenosis was relatively low with overall 22% restenosis compared to the other radioactive stent trials, despite the fact that the Cold Ends stents were 25 mm in length, while the other radioactive stents were 15 mm in length. The deleterious effects of the negative remodeling, seen at the stent edges in previous radioactive stent trials, were prevented at the Cold Ends segments. Interestingly, patients after direct stenting have a higher late loss compared to patient with predilatation followed by stenting. Even more surprisingly, the patients with a combination of direct stenting and no post-dilatation have the highest late loss during follow-up. This may support the hypothesis that edge restenosis is mainly caused by low dose radiation, rather than the degree of injury. One of the other options to reduce edge injury, currently under investigation, is the use of square shouldered balloons: They are used for radioactive stent implantation, in which the entire balloon remains within the stent during stent deployment, thereby minimizing barotrauma at the proximal and distal edges. If edge restenosis is not diminished in that trial, it will give support to the hypothesis that the low dose radiation, or dose fall-off in itself, is the main contributor of edge restenosis.

CONCLUSION

The implantation of Cold Ends radioactive stents is feasible and safe. In 14% instent restenosis of the transition zone of the radioactive to non-radioactive Cold Ends segment was observed. A pure proximal and/or distal Cold Ends restenosis was noted in 8%. Cold Ends stents therefore have a relatively low restenosis rate compared to other radioactive stents, despite the use of a longer stent. This favorable effect was obtained by preventing negative remodeling at the edges. Edge restenosis is mainly caused by the proliferative response, induced by a combination of low dose radiation and balloon injury.

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Chapter 9

Edge Restenosis After Implantation of "Hot Ends" ^{32}P Radioactive ß-Emitting Stents. The Milan and Rotterdam Experience.

Submitted

Edge Restenosis After Implantation of "Hot Ends" ^{32}P Radioactive ß-Emitting Stents The Milan and Rotterdam Experience

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ABSTRACT

Background—A high restenosis rate has been reported at the edges ("edge restenosis") of ^{32}P radioactive stents with an initial activity level up to 21 µCi. This edge effect might be due the systematic balloon injury in the first 2 mm outside the stent margins in combination with a sub-therapeutic level of radiation at the stent edges. The aim of this study was to evaluate whether an increased activity at the proximal and distal end of the stent ("hot ends") might diminish the problem of "edge restenosis", by extending the area of irradiation beyond this injured area.

Methods and Results— The "hot ends" ^{32}P radioactive ß-particle-emitting stent has a length of 18 mm. The initial radioactivity level is 2.6 µCi/mm in the proximal and distal 2 mm of the stent, and 0.57 µCi/mm in the central 14 mm of the stent. The initial total radioactivity of the stent is ~ 18.5 µCi. From July until Nov 1999, 53 patients (pts) with 56 lesions were treated in Milan (36 patients with 39 lesions) and Rotterdam (17 patients with 17 lesions) by implantation of 56 "hot ends" ^{32}P radioactive stents. There were no procedural events. At the 6-month angiographic follow-up, performed in 51 patients with 54 lesions (96%), intralesion binary restenosis was 33% (19% at the proximal edge, 7% at the distal edge, and 7% at both edges).

Conclusions—Radioactive ^{32}P "hot ends" stents did not solve the problem of edge restenosis.

Key words: radioisotopes, restenosis, stents, ultrasonics

INTRODUCTION

In patients with coronary artery disease treated with ^{32}P radioactive ß-emitting stents with an initial activity of 3 to 21 μCi, intrastent restenosis at the 6-month angiographic follow-up was ≤4% [1-3]. However, the intralesion restenosis rate was >30% due to restenosis at the stent edges ("edge restenosis") [1-3]. This edge effect might be due to the systematic balloon injury in the first 2 mm outside the stent margins in combination with a sub-therapeutic level of radiation at the stent edges [4]. The purpose of this study was to evaluate whether ^{32}P radioactive stents with an increased activity at the proximal and distal end of the stent ("hot ends") could solve the problem of "edge restenosis", by extending the area of irradiation beyond this injured area.

METHODS

Patient Population

Inclusion criteria for enrollment in this study were previously reported [1]. From July until Nov 1999, 53 patients with 56 lesions were treated in Milan (36 patients with 39 lesions) and Rotterdam (17 patients with 17 lesions) by implantation of 56 radioactive ^{32}P BX "hot ends" stents.

Radioactive Stent

The radioactive ^{32}P BX "hot ends" stent had a length of 18 mm. The initial radioactivity level (at a pre-specified date) was 2.6 μCi/mm in the proximal and distal 2 mm of the stent, and 0.57 μCi/mm in the central 14 mm of the stent. The initial total radioactivity of the stent was ~18.5 μCi. The activity reported in this study was that calculated at the date of implantation. The stent was mounted on a 20-mm-long balloon. The characteristic of the isotope (^{32}P) used in this study was previously described [1].

Procedure and Clinical Follow-Up

The technique used to implant a radioactive stent was previously reported [1]. The "hot ends"stents were implanted predilating the lesions with a nonoversized balloon, deploying the stent at 8 to 10 atm, and postdilating using a shorter balloon inflated at high pressure (>12 atm) inside the stent. After stenting, patients received long-term treatment with aspirin (325 mg daily) plus ticlopidine (250 mg twice daily) or clopidogrel (75 mg daily) for ≥3 months. Death, myocardial infarction, stent thrombosis, and target lesion revascularization (TLR) were defined as previously reported. [1,5-7]. TLR was performed on the basis of clinical symptoms and/or evidence of ischemia on exercise testing.

Angiographic and intravascular ultrasound (IVUS) analyses

The methods used for angiographic analysis and IVUS imaging, and the definitions of intrastent and intralesion restenosis were previously reported [1,5-7]. Quantitative IVUS analysis was performed by a Core Laboratory (Intravascular Ultrasound Imaging and

Cardiac Catheterization Laboratories, Washington Hospital Center, Washington, DC). Validation of IVUS measurements and reproducibility of sequential IVUS mesurements in the Washington Hospital Laboratory have been previously reported [8]. The image cross sections (1 mm apart) of the stent and of 5 mm proximal and distal to the stent were analyzed measuring postintervention (PI) and follow-up (FU) external elastic membrane (EEM), lumen, stent, and plaque (EEM minus lumen) cross sectional areas (CSA). Calculation and analysis of late lumen loss (PI-FU lumen CSA), tissue growth at the stent edges (FU-PI plaque CSA) and inside the stent (stent-lumen CSA), and remodeling (PI-FU EEM CSA) were performed in the 18 lesions with a complete serial IVUS evaluation treated by a single "hot end" stent without additional non-radioactive stents.

Statistical Analysis

Continuous variables were presented as mean±SD and categorical variables as number and percentage.

RESULTS

Patient characteristics are shown in Table 1. Angiographic and procedural characteristics are shown in Table 2. Most of the treated lesions (90%) were de novo lesions. A single stent ("hot ends") was implanted in 82% of the lesions, while an additional non-radioactive stent was required to treat a dissection in 10 lesions (18%).

Clinical Events

At 30-day follow-up no subacute stent thrombosis occurred. At 6 months, no late occlusion was seen. No patient died and only one patient experienced a myocardial infarction. TLR was performed in 13/54 (24%) lesions.

Quantitative Angiographic and IVUS Analysis

Table 3 summarizes the quantitative angiographic results. Intralesion restenosis rate was 33%, mainly located at the proximal edge, Moreover, it occurred in 50% (5/10) of the lesions treated by an additional non-radioactive stent. There was only one case (2%) of diffuse intrastent restenosis. An example of a patient with edge restenosis ("candy wrapper") 6 months after "hot ends" stent implantation is shown in Figure 1. Quantitative IVUS analysis in the 18 lesions with complete serial IVUS evaluation is shown in Figure 2: late lumen loss in the first 2 mm outside the proximal stent margin was mainly due to tissue growth, while late lumen loss ouside the distal stent margin was not higher than inside the stent.

DISCUSSION

The results of this study confirm our prior observations [1-3] on the effectiveness of ^{32}P radioactive stents in inhibiting intrastent neointimal hyperplasia. However, the "hot-ends" stents, designed to prevent edge restenosis, by extending the area of irradiation beyond the balloon-injured area outside the stent margins, did not reach this goal.

Table 1. Clinical Characteristics of the 53 Patients Studied

Male sex	40 (75)
Age, y	60.1± 9.6 (36–85)
Risk factors	
Diabetes mellitus	6 (11)
Hyperlipidemia	30 (57)
Hypertension	30 (57)
Smoking	7 (13)
Family history	21 (40)

Values are n (%) or mean±SD (range)

Table 2. Angiographic and Procedural Characteristics

No. of lesions	56
Radioactivity, μCi	14.0 ± 2.6 (9.5-18.5)
De novo lesions, n (%)	37 (90)
Vessel: - LAD	30 (54)
- LCx	12 (21)
- RCA	14 (25)
Final balloon size, mm	3.42±0.47
Final balloon length, mm	14.8±4.0
Final inflation pressure, atm	14.3±3.0
Final Balloon-to-artery ratio	1.16±0.17
No. stents/lesion	1.07±0.26
Lesions treated by a single stent	46 (82)

LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; Values are mean±SD (range) or number (%) of lesions.

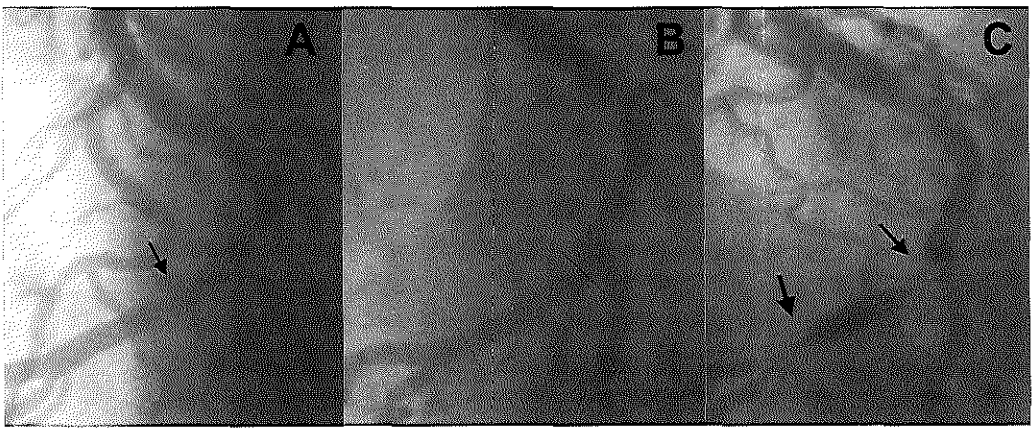

Figure 1.
Representative patient with "candy wrapper" edge effect 6 months after radioactive ^{32}P "hot ends" stent implantation. Baseline angiography (A) demonstrates a moderate 60% stenosis in the distal circumflex coronary artery. After implantation (B) of a 18-mm BX "hot ends" stent. At 6 month follow-up (C), there is absence of late loss inside stent but a tight stenosis at both stent edges. In this case, IVUS imaging demonstrated that edge restenosis was due to neointimal hyperplasia without negative remodeling.

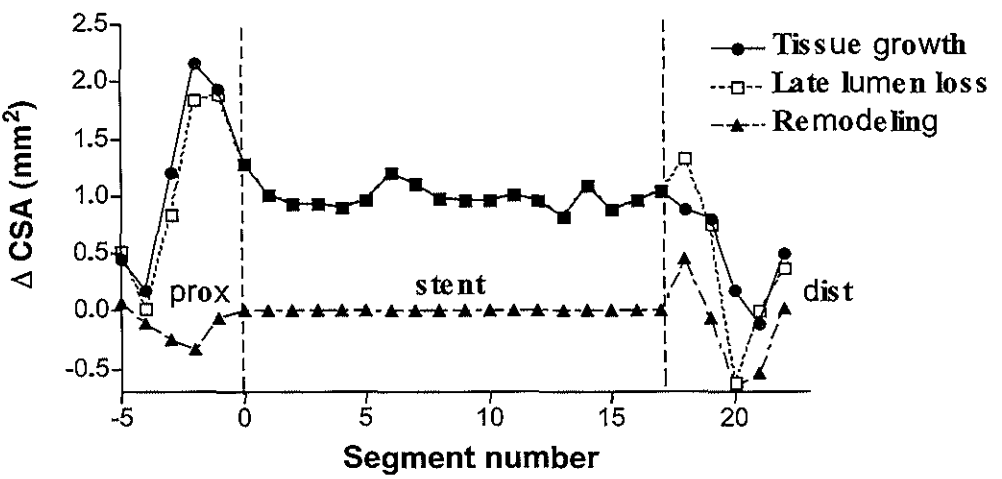

Figure 2.
Plot of mean of late lumen loss, tissue growth, and remodeling (in mm^2) in 18 lesions with complete serial IVUS evaluation treated by a single 18-mm BX "hot ends" stent. Point represents differences in CSA measured in slices 1 mm apart inside stent and in proximal and distal reference segments.

Table 3. Quantitative Angiographic Results

Preintervention	n=56
Reference diameter, mm	3.00 ± 0.61
MLD, mm	0.95 ± 0.51
Lesion length, mm	13.9 ± 4.8
Postintervention	n=56
Reference diameter, mm	3.25 ± 0.51
MLD, mm	2.95 ± 0.57
Follow-up	n=54
Reference diameter, mm	3.01 ± 0.49
MLD, mm	2.12 ± 0.94
Intralesion Restenosis, n (%)	18 (33)
- proximal edge	10 (19)
- proximal + distal edge	4 (7)
- distal edge	4 (7)

Values are mean±SD or number (%) of lesions

Mechanism of edge restenosis

The edge effect may be considered a short-term healing response to vessel wall injury beyond the stented vessel segment combined with the effects of low-dose radiation [1-4]. In this study, restenosis occurred predominantly at the proximal edge. A reason for this result may be the tendency of the operator, in order to avoid distal dissection and guarantee a good proximal stent expansion, to postdilate the stent at high pressure positioning the balloon close to the proximal margin of the stent, with an increased risk of barotrauma at this site. Another possibile explanation for the proximal edge restenosis may be the edge shear stress created by the presence of a complete inhibition of neointimal proliferation inside the stent [9].

Conclusion

Single ^{32}P radioactive ß-emitting "hot ends" stents did not solve the problem of "edge restenosis.

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Chapter 10

Square shouldered balloons. The final option to prevent edge restenosis after radioactive stent implantation.

Submitted

Square shouldered balloons. The final option to prevent edge restenosis after radioactive stent implantation.

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Aims. ^{32}P β-emitting radioactive stents with an activity of 3-24 μCi have shown edge restenosis, occurring in more than 40%, caused by neointimal hyperplasia and vessel remodeling. Edge restenosis occurs due to a combination of balloon injury and low dose radiation. Higher radiation dose, Hot Ends and Cold Ends radioactive stents did not resolve edge restenosis. The aim of this trial was to evaluate whether using square shouldered balloons to implant radioactive stents could reduce edge restenosis by reducing injury at the stent edges.

Methods and results. The radioactive ACS Multi-Link DUET stent, with a length of 23 mm, had an activity of 0.5-1.0 μCi/mm at implantation and was implanted with a specially designed square shouldered balloon, which remained purely within the stent during inflation. Preferably, direct stenting, without post dilatation was performed. Twenty-nine (97%) of the thirty patients treated for de novo native coronary artery disease had a successful radioactive stent implantation. Treated vessels were LAD (53%), RCA (30%) and LCx (17%). QCA measurements were done pre-, post-procedure and at 6-month follow-up. At 6-month clinical follow-up, TLR occurred in 8 (28%), TVR occurred in 10 (34%), non-TVR in 2 (7%) and an MI (due to a late thrombotic occlusion in a patient allergic to clopidogrel) in 1 (3%) patient. The total MACE rate was 41%. The angiographic restenosis rate was 33%, occurring all at the edges. QCA-measurments showed an RD post procedure of 3.01±0.30, MLD pre of 0.94±0.41, MLD post of 2.58±0.36, and MLD follow-up was 1.72±0.78 mm. The acute gain was 1.63±0.46 with a late loss of 0.86±0.84 mm, leading to a LLI of 0.55±0.55.

Conclusion. Using square shouldered balloons to implant radioactive stents does not prevent edge restenosis. The overall restenosis rate was 33%, occurring all at the edges. Implanting radioactive stents in patients prevents in-stent restenosis, however there is no practical solution to prevent the occurrence of edge restenosis. Therefore, radioactive stents should not be implanted in current clinical practice.

INTRODUCTION

Radioactive stents almost completely inhibited in-stent restenosis. However edge restenosis occurred in more than 40% of the patients treated with the implantation of ^{32}P radioactive stents with activities of 3-24 μCi(1-4). This edge restenosis is due to neointimal hyperplasia and negative remodeling and caused by a combination of balloon injury and low dose radiation at the edges(2-5). Several therapeutic options: higher radiation doses(4), Hot Ends and Cold Ends radioactive stents, have been investigated. Unfortunately, these did not resolve edge restenosis. The aim of this trial was to evaluate the final option to prevent edge restenosis after radioactive stenting: whether using a square shouldered balloon, which minimizes trauma at the stent edges, to implant the radioactive stent could prevent edge restenosis.

METHODS

Patient Population.

The ACS Radiation Coronary Stent System Safety Trial to Demonstrate the Reduction of Restenosis in Patients with de novo native coronary lesions was a non-randomized single-center trial to evaluate the safety and efficacy of the radioactive ACS Multi-Link DUET stent implantation. The data presented here represents all patients treated.

Patients having a de novo, native, single lesion in the target vessel with a maximum lesion length of 15 mm (treated with a 23 mm radioactive Multi-Link DUET stent) and a target vessel reference diameter of 2.5-4.0 mm, with objective evidence of ischemia were eligible. Other lesions in non-target vessels could also be treated, however not with a radioactive stent, but with a conventional (non-radioactive) stent. Exclusion criteria were: total occlusions, recent MI (CK-MB > 3 times the upper limit of normal, within 3 days of the intervention); left ventricular ejection fraction <40%; allergy or contraindication to aspirin, ticlopidine, clopidogrel or nickel; lesions located in the left main.

The Medical Ethical Committee of the University Hospital Rotterdam approved the study. All patients provided written informed consent before the procedure. The trial was conducted according to the GCP guidelines.

Radioactive stent, dosimetry and safety issues.

The radioactive ACS Multi-Link DUET stent, with a length of 23 mm, had an activity of 0.5-1.0 μCi/mm at implantation and was implanted with a specially designed square shouldered balloon, which remained purely within the stent during inflation (see Figure 1). Available stent diameters were 2.5, 3.0, 3.5 and 4.0 mm. The stent was made radioactive by Phosphorus-32(6). The initial activity of the stents was measured and thereafter the date at which the radioactivity had decreased to 0.5-1.0 μCi/mm (radioactivity level suitable for implantation) was calculated. All

personnel were trained in the appropriate handling of radioactive materials. During implantation the lucite shield enclosing the stent and the sheathed introduction system prevented exposure of the operator to the radiation of the stent. All disposable materials, which were in contact with the stent, were immediately disposed of in a plexiglas container.

Quantitative coronary angiography.

Quantitative coronary angiography (QCA) was performed pre-procedure, post-procedure, and at 6-month follow-up. Coronary angiography was performed after intracoronary administration of nitrates. The off-line analysis of at least two orthogonal projections was performed by means of the CAAS II analysis system (Pie Medical B.V., Maastricht, The Netherlands) by the angiographic corelab of Cardialysis B.V.. Calibration of the system was based on dimensions of the catheters not filled with contrast medium (7-9). The following measurements were obtained in each projection for the target vessel (sidebranch to sidebranch): minimal luminal diameter (MLD), reference diameter (RD), diameter stenosis (DS) and lesion length. Lesion length was measured by means of a computer algorithm (9). Procedural success was defined as %DS <30%. Acute gain was defined as MLD post-procedure minus MLD pre-procedure. Late loss was defined as MLD post-procedure minus MLD at follow-up. Late loss index was defined as late loss divided by acute gain (10). The target lesion was defined as the stent and both proximal and distal stent edges. The target vessel was defined as the vessel treated with the radioactive stent. Restenosis was defined as >50% DS at follow up, located within the target lesion.

Procedure and follow-up.

Patients received 250 mg aspirin and 10000 international units heparin at the start of the procedure. The ACT was maintained at >300 seconds. Whenever possible, direct stenting was performed with a nominal deployment pressure of 8-16 atmospheres. It was not allowed to exceed the rated burst pressure of the balloon (16 atm), or to expand the stent past 4.5 mm. No pre-dilatation exclusion criteria were: severely tortuous proximal vessel, angiographic evidence of calcium in the target vessel, ≥ 90° angulation at the lesion site. When predilatation was performed, it had to be performed with a balloon at least 0.5 mm smaller than the QCA-measured reference diameter and no longer than 15 mm. If an optimal angiographic result after stenting had not been achieved, additional balloon inflations with a ≤15 mm non-compliant balloon with a balloon-to-artery ratio of ≤ 1.1:1.0 was allowed to be performed, so long as the balloon diameter did not exceed the reference diameter by more than 10% and that the post-dilatation balloon did not extend beyond the edges of the stent in order to minimize balloon trauma(11). All pre-, stent-deployement and post-dilatation balloons had 1 radio-opaque marker at both edges, which

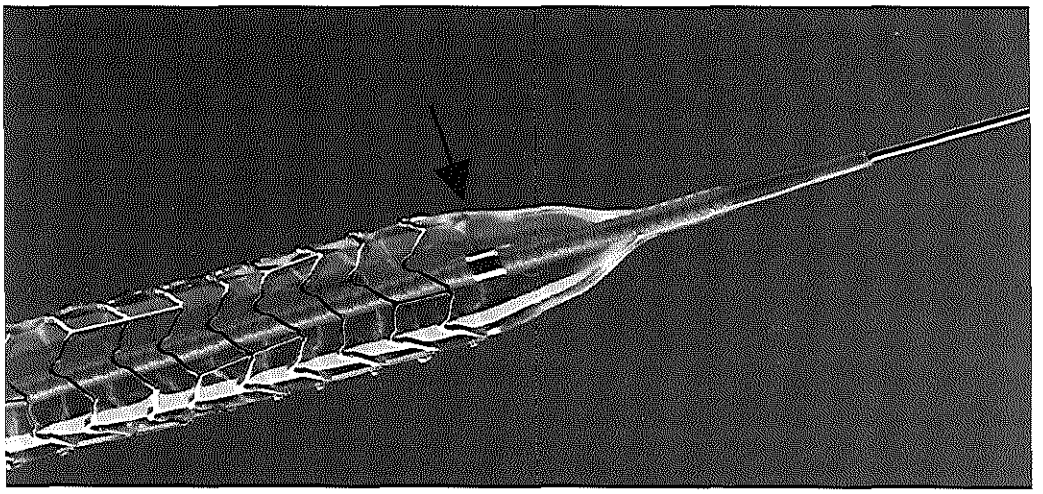

Figure 1.
Figure of a square shouldered balloon.
Immediately after the stent edge, the balloon diameter size is significantly reduced (see arrow), thereby minimizing balloon injury at the stent edges.

fluoroscopically mark the working length of the balloons. All patients received 300 mg of clopidogrel before the procedure and thereafter clopidogrel 75 mg daily during 7 months after stent implantation (or at least until 1 month after the 6-month follow-up angiography) and ≥80 mg aspirin daily indefinitely. CK and CK-MB measurements were made and the ECG was recorded at 6 and 12-18 hours post procedure in all patients.

The patients returned for 1 and 6-month clinical follow-up. An ECG was recorded at each visit. Clinical endpoints were: death, Q-wave MI (using the Minnesota code criteria (12)), non Q-wave MI (CK-MB rise >2 times normal upper limit), target lesion revascularization (TLR, reintervention of the target lesion), target vessel revascularization (TVR, revascularization of any segment of the target vessel), non-target vessel revascularization (non-TVR), sub-acute(13) and late(14) thrombotic occlusion of the target vessel. Major cardiac events (MACE) were defined as death, myocardial infarctions, repeat interventions (repeat PTCA and CABG) on both target as well as non-target vessels.

At the 6-month visit an exercise stress test was performed. Revascularization was performed on the basis of clinical symptoms and/or objective evidence of ischemia.

Statistical analysis.

Data is presented as mean ± standard deviation. Continuous data was compared by means of the two-tailed Student's t-test or linear regression when appropriate.

RESULTS

Baseline characteristics.

Baseline demographics and anginal state are shown in Table 1, lesion characteristics in Table 2.

Procedural data.

Twenty-nine of the 30 used stents were successfully implanted in 29 patients. In 1 patient, the radioactive stent could not cross the lesion for direct stenting and was removed from the patient. The protocol stated that in such a case a new radioactive stent should be used. However, a second suitably sized radioactive stent was not available. Therefore, in this patient a non-radioactive stent was implantated, following a balloon pre-dilatation. This patient was followed-up, according to the protocol, on an intention-to-treat basis, however he was left out of the final analysis of the results. In all successfully treated patients a single radioactive stent was implanted. Additional non-radioactive stents were implanted in 4 patients: in 1 patient due to a procedural dissection type D distal to the radioactive stent and in 3 patients due to a residual stenosis of >50% distal to the radioactive stent, which could not be covered by a second radioactive stent. All further procedures were uncomplicated. Direct stenting was performed in 18 patients (60%). No post dilatation, after stenting, was performed in 14 patients (48%). Procedural success was achieved in all patients.

Follow-up.

All patients were angina free at hospital discharge. The average hospital stay after the index procedure was 1.2±0.8 days. At 30-day follow-up, no subacute stent thrombosis had occurred. Twenty-three (79%) patients remained angina free, whereas 6 (21%) patients had recurrent AP. No MACE occurred during 30-day follow-up. All patients returned for 6-month clinical follow-up (see Table 3). One late stent thrombosis occurred. This patient had become allergic to clopidogrel, and despite the start of coumadin he developed a stent thrombosis. In spite of a primary PTCA, this lead to a Q-wave MI. Twelve (41%) were asymptomatic and 17 (59%) patients had Angina Pectoris Class: CCS 1 (n=5), CCS 2 (n=10), CCS 3 (n=1) and CCS 4 (n=1, the MI). Six-month angiographic follow-up was performed in 24 (83%) of the 29 patients. The remaining 5 patients, who were all both asymptomatic and had a negative stress test, refused angiographic follow-up. Eight (33%) of the 24 patients had angiographic restenosis (see Table 4). Ten (34%) of the 29 patients underwent a target vessel revascularization: there were 7 target lesion PTCAs (including the above mentioned MI-patient) and 1 CABG due to binary restenosis (DS >50%) and 2 target vessel PTCAs because of progression of atherosclerosis in the target vessel. Furthermore, there were 2 non-target vessel rePTCAs: 1 because of progression of atherosclerosis in a non-target vessel and 1 because of a treatment of a total occlusion of a non-target vessel, already present at the index procedure. The total MACE rate was 41% (12 of the 29 patients).

QCA measurements.

QCA data are presented in Table 4.

DISCUSSION

Edge restenosis is the main problem after radioactive stenting, occurring in more than 40% of the patients treated with these stents(1, 2). It is caused by a combination of balloon injury (barotrauma) and low dose radiation at the stent-edges (6, 11). This trial was conducted to investigate the final practical option to prevent edge restenosis: the use of square shouldered balloons to implant radioactive stents. Implanting a radioactive stent using these square shouldered balloons could minimize balloon injury at the stent edges, thereby reducing this edge restenosis. Furthermore, in order to decrease balloon trauma caused by predilatation, direct stenting was performed whenever possible and post-dilatation of the stent was only performed, when strictly necessary. Unfortunately, in spite of these measurements to minimize balloon injury, edge restenosis still occurred in 33%. As seen previously, edge restenosis occurred at the transition zone from the radioactive stent to the non-radioactive edge, a region located in dose fall off. This phenomenon has also been demonstrated, by our group, in an experimental setup in which half radioactive/half non-radioactive stents were implanted in the coronary arteries of pigs. The peak level of neointimal

Table 1. Baseline patient demographics and anginal status.

Gender	Male	23	(77%)
	Female	7	(23%)
Age	Average	57	
	Range	37-77	
Risk Factors	Previous MI	13	(43%)
	Previous CABG/PTCA	6	(20%)
	Diabetes Mellitus	6	(20%)
	Hyperlipidemia	22	(73%)
	Hypertension	8	(26%)
	Smoking	10	(33%)
	Family History	11	(37%)
Anginal Pectoris	Stable	11	(37%)
	Unstable	19	(63%)

hyperplasia was observed in front of the last radioactive strut, thus in the region of dose fall-off. This strongly suggested that the combination of low dose radiation, more specific dose fall-off, in association with chronic injury by the stent, implanted in non-atherosclerotic tissue, is the main determinant of edge restenosis(15). Other trials also noted that low dose radiation has a stimulatory effect, compared to higher dose radiation(16-18). Attempts to increase the radiation dose given at the site of injury, by implanting high-activity (12-21 μCi) stents(4) or Hot Ends stents, failed to reduce edge restenosis. Also the Cold Ends stents, with the aim of trying to decrease the negative remodeling part of edge restenosis, failed to significantly reduce edge restenosis. All these trials showed edge restenosis at the dose fall-off region. The results of this trial, the final option left in preventing edge restenosis: minimizing injury by using square shouldered balloons to implant the radioactive stent, perform direct stenting whenever possible, and trying to avoid post-dilatation after stenting, also showed edge restenosis, occurring in the region of dose fall-off. It must be concluded that although in-stent restenosis is prevented, there is no practical solution left to prevent edge restenosis after radioactive stent implantation. Therefore, radioactive stents should not be implanted in the current clinical practice.

Table 2. Baseline lesion characteristics.

Treated vessel	LAD	16	(53%)
	LCx	5	(17%)
	RCA	9	(30%)
Lesion type	A	1	(3%)
	B1	15	(50%)
	B2	13	(43%)
	C	1	(3%)
Vessel Disease	Single	22	(73%)
	Two	8	(27%)

Table 3. Six-month clinical follow-up.

Angina Free	12 (40%)
Target Lesion Revascularization (TLR)	12 (40%)
PTCA	11 (37%)
CABG	1 (3%)
Target Vessel Revascularization (incl. TLR)	14 (47%)
Non Target Vessel Revascularization	2 (7%)
Late Occlusion	2 (7%)
Myocardial Infarction	2 (7%)
Death	0 (0%)
Total MACE	16 (53%)

Table 4. QCA Analysis (n=24).

	Pre	Post	Follow-up
Lesion length	12±7 mm		
MLD	0.94±0.41	2.58±0.36	1.72±0.78
%DS	65±14	15±6	39±27
Ref.Diam.	2.71±0.43	3.01±0.30	2.85±0.44
Acute Gain		1.63±0.46	
Late Loss			0.86±0.84
LLI			0.55±0.55
Restenosis, n (%)			8 (33%)

%DS = % diameter stenosis, FU = follow-up, LLI = late loss index, MLD = minimum lumen diameter, Pre = pre-procedure, Post = post-procedure, Ref.Diam. = reference diameter. MLD, Ref. Diam., Acute Gain and Late Loss measurements are in mm.

CONCLUSION

Using square shouldered balloons to implant radioactive stents does not prevent edge restenosis. The overall restenosis rate was 33%, occurring all at the edges. Implanting radioactive stents in patients prevents in-stent restenosis, however there is no practical solution to prevent the occurance of edge restenosis. Therefore, radioactive stents should not be implanted in current clinical practice.

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Part 5

Intermediate term follow-up.

Chapter 11

Radioactive stents delay but do not prevent in-stent neointimal hyperplasia.

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Radioactive Stents Delay but Do Not Prevent In-Stent Neointimal Hyperplasia

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Background—Restenosis after conventional stenting is almost exclusively caused by neointimal hyperplasia. β-Particle–emitting radioactive stents decrease in-stent neointimal hyperplasia at 6-month follow-up. The purpose of this study was to evaluate the 1-year outcome of ^{32}P radioactive stents with an initial activity of 6 to 12 μCi using serial quantitative coronary angiography and volumetric ECG-gated 3D intravascular ultrasound (IVUS).

Methods and Results—Of 40 patients undergoing initial stent implantation, 26 were event-free after the 6-month follow-up period and 22 underwent repeat catheterization and IVUS at 1 year; they comprised half of the study population. Significant luminal deterioration was observed within the stents between 6 months and 1 year, as evidenced by a decrease in the angiographic minimum lumen diameter (−0.43±0.56 mm; P=0.028) and in the mean lumen diameter in the stent (−0.55±0.63 mm; P=0.001); a significant increase in in-stent neointimal hyperplasia by IVUS (18.16±12.59 mm^3 at 6 months to 27.75±11.99 mm^3 at 1 year; P=0.001) was also observed. Target vessel revascularization was performed in 5 patients (23%). No patient experienced late occlusion, myocardial infarction, or death. By 1 year, 21 of the initial 40 patients (65%) remained event-free.

Conclusions—Neointimal proliferation is delayed rather than prevented by radioactive stent implantation. Clinical outcome 1 year after the implantation of stents with an initial activity of 6 to 12 μCi is not favorable when compared with conventional stenting. (***Circulation.*** **2001;103:14-17.)**

Key Words: radioisotopes ■ restenosis ■ stents ■ angiography

Implantation of ^{32}P radioactive stents with activities ranging from 3.0 to 12 μCi in coronary artery lesions has been reported to inhibit neointimal hyperplasia within the stent at 6-month follow-up.[1,2] The major limitation of this therapy is significant renarrowing at the stent edges, which is called the "candy wrapper" or "edge effect."[1] Catheter-based radiation significantly reduces the recurrence of restenosis 6 months after percutaneous transluminal coronary angioplasty for in-stent restenosis, but 3-year follow-up reveals greater luminal deterioration in γ-radiation–treated patients.[3,4] Such findings indicate the need for longer follow-up beyond the traditional 6 months in patients treated with intracoronary radiation. The purpose of this study was to assess late results after the implantation of radioactive stents using repeat catheterization with quantitative coronary angiography and 3D intravascular ultrasound (IVUS) at 1 year.

Methods

Patient Population

The European ^{32}P Dose-Response Trial was a nonrandomized multicenter trial evaluating the safety and efficacy of implanting radioactive stents with activity levels of 3 to 12 μCi in single, native coronary artery lesions. All stents were implanted in de novo lesions, except for 1 case of in-stent restenosis. For the purposes of this analysis, this case was excluded. Other inclusion and exclusion criteria, as well as immediate and 6-month results, were previously reported.[1,2] Only patients undergoing 6-month angiographic and IVUS follow-up who did not experience major adverse cardiac events during the first 6 months were included. The study was performed in accordance with the Declaration of Helsinki and the European Guidelines for Good Clinical Practice. Ethical approval was provided by the Medical Ethical Committee of the University Hospital Rotterdam. All patients gave written, informed consent.

Radioactive Stent

The BX Isostent (^{32}P) (Isostent Inc), which is 15 mm in length and 3.0 or 3.5 mm in diameter, was used. The initial activity of the stents was measured and, thereafter, the date at which the radioactivity would have decreased to 6 to 12 μCi was calculated.

Procedure and Clinical Follow-Up

Procedural details have been published previously.[5] All patients received either 250 mg of ticlopidine BID or 75 mg of clopidogrel per day for 3 months after stent implantation and 80 mg of aspirin per day indefinitely. Revascularization was performed on the basis of clinical symptoms and/or evidence of ischemia on exercise testing. Clinical end points were death, Q-wave myocardial infarction, non–Q-wave myocardial infarction (creatine kinase-MB rise >2

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TABLE 1. Baseline Characteristics of the 22 Patients Studied

Male sex	20 (91)
Age, y	57 (38–73)
Risk factors	
Previous MI	12 (55)
Diabetes mellitus	3 (14)
Hyperlipidemia	18 (82)
Hypertension	9 (41)
Smoking	8 (36)
Family history	7 (32)
CCS class 3/4	15 (68)
Treated vessel	
LAD	12 (55)
LCx	5 (22.5)
RCA	5 (22.5)
Lesion type	
A	2 (9)
B1	10 (45.5)
B2	8 (36.5)
C	2 (9)
Lesion length, mm	10±3

Values are n (%), mean (range), or mean±SD. MI indicates myocardial infarction; CCS, Canadian Cardiovascular Society; LAD, left anterior descending coronary artery; LCx, left circumflex artery; and RCA, right coronary artery.

times normal upper limit), target vessel revascularization, non–target vessel revascularization, and early and late thrombotic occlusion of the target vessel.

Angiographic and IVUS Procedures

Angiography in multiple projections was performed before the procedure, after stenting, and at 6-month and 1-year follow-up. The stented vessel segments were examined with quantitative coronary angiography (CAAS II analysis system,[6,7] Pie Medical BV) and mechanical IVUS (CardioVascular Imaging System). IVUS images were acquired to coincide with the peak of the R wave by using an ECG-triggered pullback device with a stepping motor at 0.2 mm/step. This system eliminates the artifacts caused by the movement of the heart during the cardiac cycle.[8] The ECG-gated image acquisition and digitization was performed by a workstation designed for 3D reconstruction (EchoScan, Tomtec). A Microsoft Windows-based contour detection program was used for the volumetric 3D analysis.[8]

Core Laboratory Analysis Procedures

Quantitative coronary angiography using at least 2 orthogonal projections was performed. For analytical purposes, the following 3 regions of interest were defined: (1) stent, (2) target lesion, and (3) target vessel. The stent included only the radioactive stent. The target lesion was defined as the stent and 5 mm proximal and 5 mm distal to the edge. The target vessel was defined as the target lesion and the remaining segments of the treated vessel. Target lesion restenosis was defined as >50% diameter stenosis, located within the target lesion, at follow-up.[9] Edge restenosis was defined as >50% diameter stenosis, located at the proximal and/or distal edge, at follow-up.

Quantitative IVUS analysis of the stent and 5 mm proximal and distal to the stent was performed. Lumen and stent boundaries were detected using a minimum cost algorithm. Total stent and lumen volumes were calculated as previously described.[8] Neointimal volume was calculated as stent volume minus luminal volume. Feasibility, reproducibility, and interobserver and intraobserver variability of this system have been validated in vitro and in vivo.[8]

Statistical Analysis

Data are presented as mean±SD. Continuous data were compared using repeated measures ANOVA or a 2-tailed Student's t test as appropriate.

Results

Baseline demographics and lesion characteristics are shown in Table 1. Between 6 months and 1 year, target lesion revascularization and target vessel revascularization were performed in 4 patients (18%) and 5 patients (23%), respectively. No late occlusion was seen. No patient died or experienced myocardial infarction. In total, 21 of 40 patients (53%) were event-free through the 1-year follow-up.

Quantitative Coronary Angiography and IVUS Measurements

Quantitative coronary angiography data, presented as a subsegmental analysis of the stent area and the edges, are shown in Table 2. A significant decrease in the minimum and mean lumen diameters was noted between 6 months and 1 year (P=0.028 and P=0.001, respectively) compared with both edges. The late loss of mean lumen diameter was significantly larger after 6 months than before 6 months. Furthermore, in 11 patients (50%), the minimum lumen diameter at the edge at 6 months was detected within the stent at 1 year ("migration" from the stent edge to within the stent). Lesion progres-

TABLE 2. Subsegmental Quantitative Coronary Angiography Analysis

				Late Loss			
	Baseline	6 Months	1 Year	Baseline to 6 Months	6 Months to 1 Year	Total	P Between Periods
Minimum lumen diameter, mm							
Proximal edge	2.92±0.53	2.23±0.73*	2.08±0.50	0.69±0.80†	0.15±0.51‡	0.84	0.060
Stent	2.50±0.47	2.36±0.47*	1.93±0.52*	0.14±0.52†	0.43±0.56‡	0.57	0.16
Distal edge	2.29±0.61	2.17±0.58	2.08±0.49	0.36±0.49†	0.09±0.49‡	0.45	0.9
Mean lumen diameter, mm							
Proximal edge	3.19±0.56	2.73±0.57*	2.50±0.40*	0.39±0.62§	0.22±0.51‖	0.61	0.33
Stent	3.12±0.42	3.09±0.58	2.54±0.41*	0.03±0.62§	0.55±0.63‖	0.68	0.041
Distal edge	2.64±0.56	2.51±0.56	2.36±0.50	0.12±0.49§	0.16±0.52‖	0.28	0.9

*P<0.05, †P=0.0041, ‡P=0.025, §P=0.028, ‖P=0.001 by ANOVA.

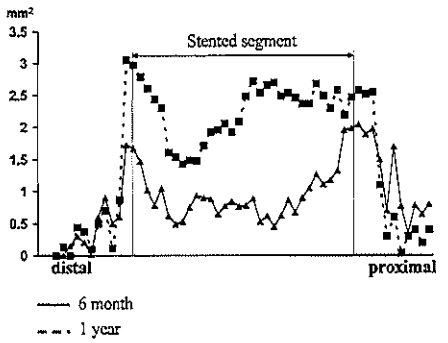

Figure 1. Mean neointimal area in stent at 6 months (■) and 1 year (▲) using IVUS.

sion to >50% diameter stenosis was observed in 5 patients. This was due to a progression of in-stent restenosis in 4 patients and a progression of a proximal stent-edge lesion in the other.

IVUS was completed in 19 patients; omissions were due to equipment failure[2] or patient clinical instability.[1] IVUS analysis demonstrated a significant increase in neointimal hyperplasia between 6 months and 1 year (18.16±12.59 mm^3 to 27.75±11.99 mm^3; increase of 52.8%; P=0.001), mainly in the mid and distal portions of the stent (Figure 1). An increase in neointimal hyperplasia >25% (range, 25% to 360%) occurred in 12 cases (63%), as shown in Figure 2. No change in lumen volume was noted at the stent edges between 6 months and 1 year.

Radiation Doses

The radioactive stents had a mean activity of 8.6±1.6 μCi at implantation and delivered 58±10 Gy to a depth of 1 mm from the stent at 100 days, with a dose rate of >15cGy/h. There was no correlation between stent activity or delivered dose and changes in minimum or mean lumen diameter at 6-month or 1-year follow-up.

Discussion

A worrying late progression of in-stent neointimal hyperplasia was observed between 6 months and 1 year after the implantation of radioactive stents, leading to target vessel or lesion reintervention in 5 of 26 patients (19%) who had been event-free at 6 months. The event-free rate at 1 year after the implantation of 6 to 12 μCi radioactive stents was 21 of 40 patients (53%), which compares poorly to the expected outcome after the implantation of a nonradioactive stent.[10]

In contrast to the tissue growth seen in malignancy, the DNA synthesis that occurs after nonradioactive stenting in experimental models terminates after 6 weeks.[11] At this time point, the activity of the radioactive stent used in this study would have been sufficient to inhibit cellular proliferation. Thereafter, the majority of lumen deterioration occurs in the first 3 months after conventional stent implantation, with minimal change between 6 months and 1 year,[12–14] and actual regression of neointimal hyperplasia between 1 and 3 years after stenting.[15] This latter phenomenon has been attributed to a reduction in the proteoglycan content of hyperplastic tissue.[16] Accordingly, the findings reported here of "breakthrough" or "rebound" hyperplasia causing further lumen deterioration between 6 months and 1 year must be interpreted as being specific to the effects of radioactivity, presumably due to a fall- off in radiation levels. The observation that the radioactive stent may provide a substrate for atherosclerosis may well have been predicted by Carter et al's porcine model.[17]

Because no significant stenosis progression was observed at the stent edges among our patients, the candy wrapper effect may be considered a short-term healing response to vessel wall injury beyond the stented vessel segment combined with the effects of low-dose radiation.[18,19]

Unexpected late luminal deterioration has also been reported between 6 months and 3 years among patients treated by catheter-based γ-radiation after repeat intervention for in-stent restenosis (mean loss of 0.37 mm with 4 of 17 patients [26%] progressing to restenosis [diameter stenosis >50%]), compared with no major changes in the placebo group.[4] The difference in the time frame of this virtual "rebound hyperplasia" between radioactive stenting and catheter-based γ-radiation therapy may be a function of the biological effects of and response to the type and dosage of radiation administered. Alternatively, late loss may also have

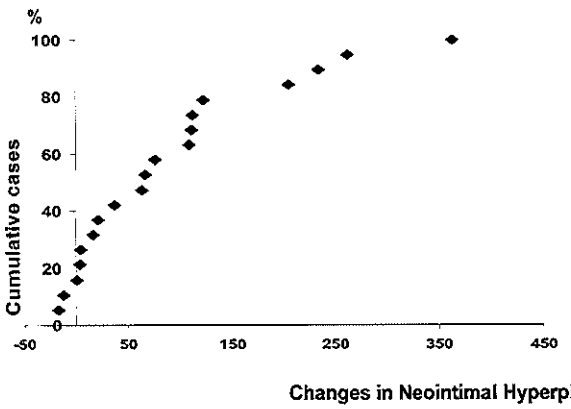

Figure 2. Cumulative distribution curve of percent changes in late neointimal growth after 6 months, as measured by IVUS.

occurred between 6 months and 1 year and remained subclinical in the catheter-based study.

Conclusions

Neointimal hyperplasia is delayed rather than prevented by radioactive stent implantation. The combination of this phenomenon of rebound hyperplasia with the established phenomenon of edge restenosis calls into question the clinical applicability of radioactive stenting using current approaches.

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Chapter 12a

Summary and conclusions.

Summary

The objective of the research work presented in this thesis was to evaluate the clinical use of radioactive stents to control restenosis. Clinical trials were conducted for evaluation. The contents of the thesis can be presented by grouping various sections into the following parts:

I) The concept of brachytherapy and its use to treat several diseases were outlined in chapter 2 of the thesis. Radiotherapy is a proven and successful treatment of several benign diseases and solid malignancies. Usually radiation doses of 7-10 Gy are used, which efficiently inhibit fibroblastic activity, without influencing the normal healing process, and without causing significant morbidity during long term follow-up. The use of this novel treatment was perceived to be a promising treatment for the prevention of restenosis. Several catheter-based trials have in the mean time proven its efficacy.

II) The evaluation of several radiation doses for their safety and efficacy after the implantation of radioactive stents. The results of the IRIS trial, which investigated stents with a radioactivity of 0.75-1.5 μCi at the time of implantation, were described in chapter 3. The trial showed that the implantation of radioactive stents in patients with coronary artery disease was feasible and safe. However, a restenosis rate similar to conventional (non-radioactive) stents was observed. Chapter 4 covered a part of a multi-center trial (the European Dose Finding study), which investigated 3 groups of stents with a radioactivity of respectively, 1.5-3.0, 3-6 and 6-12 μCi at the time of implantation. The in-stent neointimal hyperplasia was observed to be inhibited in a dose-dependently manner. In the 6-12 μCi group in-stent restenosis was observed to be 0%. However, a new phenomenon, called edge restenosis, was observed. It occurred in more than 30% of the patients. The edge restenosis was observed at the egde(s) proximal and/or distal to the stent and considered to be a result of a combination of balloon injury and low dose radiation at the edges of the stent.

III) The mechanisms and side effects of the radioactive stents were investigated and presented. Chapter 5 studied the differences between vascular remodeling in 4 kinds of treatment groups: 1) conventional (non-radioactive) stent implantation, 2) catheter based radiation therapy followed by conventional stent implantation, 3) low activity radioactive stent implantation, and 4) high activity radioactive stent implantation. No differences in plaque or total vessel volume were observed behind the stents in the radiation groups (groups 2, 3, and 4). Significant increases in plaque behind the stent and in total vessel volume (positive remodeling) were observed in the group that underwent catheter based radiation therapy followed by conventional stent implantation (group 2). All 4 groups demonstrated significant lumen loss at the stent edges, however edge

restenosis was observed only in the group subjected to high activity stent implantation (group 4). This edge restenosis was probably due to an increase in plaque and, to a lesser degree, due to negative remodeling. The mechanism of restenosis after the implantation of cold ends stents - radioactive stents extended with non-radioactive parts – was studied in chapter 6. An increased neointimal hyperplasia was observed in the (in-stent) cold ends segments, while neointimal hyperplasia was inhibited in the center (radioactive) part of the stent. The black hole phenomenon (chapter 7), a new entity seen after brachytherapy, was first observed as an echolucent tissue on intravascular ultrasound (IVUS). Atherectomy samples collected from the coronary arteries of patients treated with radioactive stents demonstrated that the black holes were actually predominately proteoglycans with a noticeable lack of collagenous tissue. This tissue might be the precursor of atherogenic tissue and could explain the observed lumen loss between 6 and 12 months after radioactive stent implantation in the patients.

IV) This part was aimed at finding a solution for edge restenosis, the main problem after radioactive stenting. A multicenter trial on the use of Cold Ends radioactive stents was conducted for this purpose (chapter 8). The rationale behind the use of these stents was the observed negative remodeling noted at the edges of radioactive stents. It was hypothesized that extending the radioactive stent with non-radioactive (cold ends) parts could reduce edge restenosis by preventing negative remodeling. The trial was partially successful, since these stents with a length of 25 mm had a restenosis rate of only 22%. This can certainly be contributed to the prevention of negative remodeling by the cold ends parts of these stents. A further hypothesis was investigated (chapter 9), which stated that edge restenosis might be due to the systematic balloon injury in the first 2 mm outside the stent margins in combination with a sub-therapeutic level of radiation at the stent edges. The purpose of the trial was to evaluate whether Hot Ends radioactive stents - stents with an increased activity at the proximal and distal end of the stent - could solve the problem of edge restenosis, by extending the area of irradiation beyond this injured area. This treatment however did not succeed in reducing edge restenosis. Therefore, the final option to prevent edge restenosis was explored: the use of square shouldered balloons to implant radioactive stents (chapter 10). Conventional balloons would normally cross the stent edges, thereby causing trauma at the edges. Square shouldered balloons however remained strictly within the stent during implantation. This treatment minimized balloon injury at the stent edges, thereby possibly reducing edge restenosis. Furthermore, in order to decrease balloon trauma caused by predilatation, direct stenting was performed whenever possible and post-dilatation of the stent was only performed, when strictly necessary. Unfortunately, despite these measures to minimize balloon injury, the edge restenosis rate was still high. Edge restenosis occurred in 33% of the cases. Edge restenosis was observed to occur at the transition zone from the radioactive stent to the non-radioactive edge, a region located in dose fall off.

V) The results of the intermediate follow-up after radioactive stenting were presented in chapter 11. The edges of the stents were the major problem at the 6-month follow-up and remained unchanged at the 12-month follow-up. At the 6-month follow-up in-stent neointimal hyperplasia was hardly observed in the radioactive stents, however at the 12-month follow-up a remarkable increase in the in-stent neointimal hyperplasia was observed. Therefore, it was concluded that radioactive stents delayed but did not prevent in-stent neointimal hyperplasia.

Conclusions

Radioactive stents have the ability to prevent in-stent restenosis, but far too many side effects may arise with the use of these devices. Due to the significant side effects, namely: edge restenosis, black holes, and late stent thrombosis, the implantation of these stents should not be undertaken. Even if these problems could be solved, which is highly improbable, especially the problem of edge restenosis, the delayed in-stent restenosis, which was observed at 12-month follow-up, is a seriously discouraging factor to the use of radioactive stents. Therefore, this thesis comes to the following final conclusion: radioactive stents should not be implanted in the current clinical practice.

Chapter 12b

Samenvatting en conclusies.

Samenvatting

Het doel van het onderzoekswerk, welke gepresenteerd werd in dit proefschrift, was de evaluatie van het klinisch gebruik van radioactieve stents om restenose te verminderen. Klinische studies werden verricht ter evaluatie. De inhoud van dit proefschrift kan gepresenteerd worden door de verschillende secties te groeperen in de volgende delen:

I) Het concept van de brachytherapie en haar gebruik om verschillende ziektes te behandelen. Deze werden uiteengezet in hoofdstuk 2 van dit proefschrift. Radiotherapie is een bewezen en succesvolle behandeling voor verschillende benigne aandoeningen en solide maligniteiten. Tijdens de behandelingen werden doses van 7-10 Gy gebruikt, welke effectief fibroblastische activiteit inhiberen, zonder invloed te hebben op het normale genezingsproces en zonder een significante morbiditeit te veroorzaken gedurende lange termijn follow-up. Deze nieuwe behandeling werd aangemerkt als een veelbelovende behandeling voor de preventie van restenose. Verschillende catheter-gebaseerde brachytherapie studies hebben ondertussen haar effectiviteit bewezen.

II) De evaluatie van verschillende radiatie doses voor veiligheid en effectiviteit na de implantatie van radioactieve stents. De resultaten van de IRIS studie, welke radioactieve stents onderzocht met een activiteit van 0,75-1,5 μCi ten tijde van de implantatie, werden beschreven in hoofdstuk 3. De studie toonde aan dat de implantatie van radioactieve stents in patiënten met coronaire hartziekte toepasbaar en veilig is. Er werd echter een restenose percentage vergelijkbaar met conventionele (niet-radioactieve) stents waargenomen. Hoofdstuk 4 behandelde een gedeelte van een multi-centrum onderzoek (de European Dose Finding studie), welke 3 groepen van stents met een radioactiviteit van respectievelijk 1,5-3, 3-6 en 6-12 μCi ten tijde van de implantatie onderzocht. Er werd waargenomen dat de in-stent neointimale hyperplasie op een dosis afhankelijke manier geïnhibeerd werd. In de 6-12 μCi groep was de in-stent restenose 0%. Er werd een nieuw fenomeen gevonden, genaamd edge restenose (randen restenose). Deze trad op in meer dan 30% van de patiënten. De edge restenose werd waargenomen aan de proximale en/of distale rand van de stent en werd beschouwd het resultaat te zijn van een combinatie van ballon trauma en bestraling met lage dosis aan de randen van de stent.

III) Het mechanisme en de bijwerkingen van de radioactieve stents werden onderzocht en gepresenteerd. Hoofdstuk 5 onderzocht de verschillen tussen de vaatremodellering in 4 soorten behandelingsgroepen: 1) conventionele (niet-radioactieve) stent implantatie, 2) catheter-gebaseerde bestralingstherapie gevolgd door conventionele stent implantatie, 3) lage activiteit radioactieve stent implantatie en 4) hoge activiteit radioactieve stent implantatie. Er werden geen verschillen tussen de plak of het totale vat volume achter de stents waargenomen in de bestralingsgroepen (groepen 2, 3 en 4). Er werd echter een significante stijging waargenomen in de plak achter de stent and in het totale vat

volume (positieve remodellering) in de groep die een catheter-gebaseerde bestraling gevolgd door een conventionele stent plaatsing had ondergaan (groep 2). Alle 4 groepen demonstreerden een significant lumen verlies aan de randen van de stent. Edge restenose werd echter alleen gezien in de groep welke een hoge activiteit stent implantatie had ondergaan (groep 4). Deze edge restenose was waarschijnlijk het gevolg van een toename in plak en, voor een kleiner gedeelte, negatieve remodellering. Het mechanisme van restenose na het plaatsen van cold ends stents – radioactieve stents verlengd met niet-radioactieve gedeeltes – werd bestudeerd in hoofdstuk 6. Een toegenomen neointimale hyperplasie werd waargenomen in de (in-stent) cold ends segmenten, terwijl de neointimale hyperplasie geïnhibeerd werd in het (centrale) radioactieve gedeelte van de stent. Het zwarte gat (black hole) fenomeen (hoofdstuk 7), een nieuwe entiteit welke optrad na brachytherapie, werd voor het eerst waargenomen als echolucent weefsel op het intravasculair ultrageluidsonderzoek (IVUS). Atherectomie monsters verzameld uit de kransslagaders van patiënten behandeld met radioactieve stents toonden aan dat de zwarte gaten voornamelijk proteoglycanen met een opmerkelijk gebrek aan collageen weefsel waren. Dit weefsel zou de voorloper kunnen zijn van atherogeen weefsel en zou het lumen verlies kunnen verklaren welke optreedt tussen de 6 en 12 maanden na radioactieve stent implantatie in de patiënten.

IV) Dit deel had als doel een oplossing voor de edge restenose, het voornaamste probleem na radioactieve stent implantatie, te vinden. Een multicentrum onderzoek over het gebruik van Cold Ends radioactieve stents werd uitgevoerd voor dit doel (hoofdstuk 8). De aanzet tot het gebruik van deze stents vormde de negatieve remodellering, welke was waargenomen aan de randen van de stent. De hypothese was dat door verlenging van de radioactieve stent met niet-radioactieve (cold ends) gedeelten de edge restenose zou kunnen verminderen door de preventie van negatieve remodellering. Het onderzoek bleek slechts gedeeltelijk succesvol, aangezien deze stents met een lengte van 25 mm een restenose percentage hadden van 22%. Dit kon zeker toegeschreven worden aan de preventie van negatieve remodellering door de cold ends gedeeltes van deze stents. Een andere hypothese werd onderzocht (hoofdstuk 9), welke als uitgangspunt had dat edge restenose mogelijk veroorzaakt werd door de systematische beschadiging door de ballon in de eerste 2 mm buiten de stent randen, in combinatie met een sub-therapeutisch niveau van de bestraling ter plekke van de randen van de stent. Het doel van dit onderzoek was te evalueren of Hot Ends radioactieve stents – stents met een verhoogde activiteit aan het proximale en distale uiteinde van de stent – het probleem van edge restenose konden oplossen door het gebied dat bestraald werd uit te breiden tot voorbij dit beschadigd gebied. Deze behandeling slaagde er echter niet in edge restenose te verminderen. Daarom werd de laatste mogelijkheid voor de preventie van randen restenose onderzocht: het gebruik van "square shouldered balloons" om radioactieve stents te implanteren (hoofdstuk 10). Conventionele ballonnen passeerden normaliter

de randen van de stent en veroorzaakten daardoor trauma aan de randen. "Square shouldered balloons" bleven echter puur in de stent. Deze behandeling minimaliseerde de ballon trauma aan de randen van de stent met mogelijk daardoor een vermindering van de edge restenose. Bovendien werd de ballon trauma veroorzaakt door een predilatatie verminderd door, indien mogelijk, het direct plaatsen van een stent en werd een post dilatatie van de stent alleen verricht indien strikt noodzakelijk. Ondanks al deze maatregelen om de ballon trauma te minimaliseren was het edge restenose percentage nog steeds hoog. Edge restenose trad op in 33% van de gevallen en werd waargenomen op de overgang van de radioactieve stent naar de niet-radioactieve rand, een gebied van bestralingsdosisverval.

V) De resultaten van de intermediaire follow-up na het plaatsen van een radioactieve stent werden gepresenteerd in hoofdstuk 11. De randen van de stent waren het voornaamste probleem bij de 6-maands controle en deze bleven onveranderd bij de 12-maands controle. Neointimale hyperplasie werd nauwelijks waargenomen in de radioactieve stent bij de 6-maands controle, echter bij de 12-maands controle werd een duidelijke toename gevonden. Derhalve werd geconcludeerd dat radioactieve stents in-stent neointimale hyperplasie konden vertragen, maar niet voorkomen.

Conclusies

Radioactieve stents hebben de mogelijkheid om in-stent restenose te voorkomen, maar er treden te veel bijwerkingen op bij het gebruik van deze instrumenten. Significante bijwerkingen, zijnde: edge restenose, zwarte gaten en late stent thrombose, maken dat de implantatie van deze stents niet zou moeten plaatsvinden. Zelfs indien deze problemen opgelost zouden kunnen worden, hetgeen hoogst onwaarschijnlijk is, zeker gezien het probleem van de edge restenose, is de vertraagde in-stent restenose, welke bij de 12-maands controle werd waargenomen, een serieuze ontmoedigende factor voor het gebruik van radioactieve stents. Al met al komt dit proefschrift tot de volgende slotsom: radioactieve stents moeten niet geïmplanteerd worden in de huidige klinische praktijk.

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Curriculum Vitae

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In 1990 behaalde hij het VWO diploma aan het Develstein College te Zwijndrecht. In datzelfde jaar begon hij met de studie geneeskunde aan de Erasmus Universiteit te Rotterdam. In 1996 behaalde hij het artsexamen. Daarna is hij van oktober 1996 tot juni 1997 AGNIO cardiologie geweest in achtereenvolgens het AZR "Dijkzigt" en het Zuider Ziekenhuis. Vanaf juni 1997 tot maart 2001 was hij studiecoördinator van de afdeling interventiecardiologie van het Thoraxcentrum Rotterdam in het AZR "Dijkzigt". Op 1 maart 2001 is hij begonnen als arts assistent geneeskundige op de afdeling Interne Geneeskunde van het Albert Schweitzer Ziekenhuis te Dordrecht (opleiders dr. J. van der Meulen en dr. A.C.M. van Vliet), als onderdeel van de opleiding tot cardioloog, welke vanaf 1 maart 2003 zal worden voortgezet aan het Universitair Medisch Centrum St. Radboud te Nijmegen (opleider Prof. dr. F.W.A. Verheugt).