Intracoronary brachytherapy

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Abstract

Restenosis following PTCA or intracoronary stent insertion remains the greatest challenge to interventional cardiology. Intracoronary brachytherapy may use either beta- or gamma-radiation. The target cells are most likely in the adventitial layer of the vessel wall. The principle of using brachytherapy post-angioplasty to reduce restenosis has been proven in animal models. Multiple randomised trials have shown brachytherapy to be the current optimal therapy to treat in-stent restenosis. The data for the use of intracoronary radiation for treatment of *de novo* coronary lesions are less strong. Potential complications of brachytherapy include 'edge effect' and 'late late stent thrombosis'. These problems are being minimised with the use of long sources and prolonged antiplatelet therapy. Drug delivery stents may challenge the role of brachytherapy in preventing and treating restenosis in the near future.

Key words: brachytherapy, beta-radiation, gamma-radiation, in-stent stenosis, restenosis, coronary arteries, stents, angioplasty.

Introduction

The Achilles' heel of percutaneous transluminal coronary angioplasty (PTCA) has traditionally been abrupt vessel closure (occurring in 2–8% of patients)[1] and the high incidence of recurrence (both clinical [13–16%] and angiographic [22–32%]) even for 'simple' lesions.[2] The early use of intracoronary stents has greatly reduced the incidence of abrupt vessel closure during PTCA and the Stress/BENESTENT studies showed the benefit of this type of device in reducing both angiographic and clinical restenosis following PTCA.[2] However, the population of patients studied in the Stress/BENESTENT studies was highly selected (focal lesions <15 mm in length, reference diameter >3 mm, non-ostial, no thrombus, non-bifurcational, non-vein graft with elective deployment) and would account for only 15–20% of patients undergoing PTCA at our own institution. The results of intracoronary stenting in 'non-Stress/BENESTENT' lesions are less impressive, with angiographic and clinical restenosis rates in the 30–50% range.[3]

The newly produced disease process of 'in-stent restenosis' is also extremely difficult to treat. The use of simple techniques in this setting, such as re-dilatation by PTCA and re-stenting, is associated with a recurrence rate of 50–80%, especially in diffuse disease processes.[4] Restenosis remains, therefore, the greatest challenge to interventional cardiology, following either PTCA or intracoronary stent insertion.

The use of radiation therapy to treat a proliferative, non-malignant disease process is established in the treatment of keloid scars.[5] If restenosis following coronary angioplasty is considered to be a similar process then the use of radiation would seem a reasonable approach in this setting.

Basic concepts of intra-vascular radiation therapy

Brachytherapy refers to radiation therapy with a radioactive source placed in or near the target cell (in this case intracoronary brachytherapy). Broadly speaking, two types of radiation source are currently used for intracoronary brachytherapy, namely those which deliver either beta (β) or gamma (γ) radiation. β-particles are high-speed electrons that are emitted from the nucleus of an unstable atom. They are high energy but have a low penetration so that the dose fall-off distant to the source is rapid. γ-rays are high-energy photons, again emitted from the nucleus of an unstable atom. The penetration of γ-rays is much higher than β, meaning that the dose fall-off is much lower. The unit of dose of radiation is the gray (Gy) and refers to the mean energy imparted by ionising radiation to matter in a given volume divided by the mass of the matter in that volume.

The mechanism of action of both β- and γ-radiation is identical. Radiation disrupts DNA by strand and cross-link breakage. This leads to cell death the next time the cell divides. The target cell for brachytherapy treatment is not entirely clear although the most likely candidate appears to be the myofibroblasts in the adventitial layer which migrate into the intima and transform into smooth muscle cells.[6] The dose of radiation appears crucial: too low a dose is ineffective or even stimulatory to neointimal growth, and too high a dose is potentially associated with aneurysm formation due to thinning and weakening of the vessel wall. Dosimetry is undoubtedly more difficult with the β-sources because of the low penetration of the energy. Despite this, the clinical results appear equal for these two types of radiation.

The use of γ-radiation has some practical difficulties because

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of the need for more extensive radiation protection measures and the increased total body dose to the patient. In Europe the majority of centres performing this type of work have decided to use β-radiation.

Animal data

The principle of using brachytherapy post-angioplasty to reduce restenosis has been proven in the animal model. This is true for both β- and γ-radiation and also in a number of different animal models.[7,8] However, it is likely that doses that have been proven effective in the animal model could prove ineffective in the human because the disease process is less predictable and often markedly eccentric.[9] There has also been some criticism of the animal models because of the short term follow-up used and the young age of the animals (this may have some influence on radiation sensitivity). Despite these concerns, human studies were commenced following encouraging results in the animal model.

Initial clinical human trials

In 1994, Condado *et al*. performed the first intracoronary brachytherapy cases in the world, using the γ-isotope iridium-192 (Ir-192), and reported a restenosis rate of 28.6% at six months.[10] More recently, the five-year follow-up data have been reported, with no change in the angiographic restenosis rate (data presented at Cardiovascular Radiation Therapy V, Washington, Feb 5–7, 2001). Despite the use of relatively high doses of radiation and the presence of one new pseudoaneurysm at early follow-up, no progression of aneurysm formation or late adverse effects have been seen at five years in this group of patients.

Gamma in-stent restenosis trials

The SCRIPPS (the Scripps Coronary Radiation to Inhibit Proliferation Post Stenting) trial was a landmark study which reported favourable results for the use of intracoronary γ-brachytherapy (with Ir-192) for restenosis in the human.[11] Two thirds of the patients presented with in-stent restenosis, a particularly high-risk group for repeat restenosis following further interventional therapies. Six-month angiographic restenosis showed a 16.7% restenosis rate in the radiation group as compared to 53.6% in the placebo group. Similar impressive results were also seen in the single-centre Washington Radiation for In-Stent restenosis Trial (WRIST)[12] and the multi-centre Gamma-1 Trial.[13] In both the WRIST and Gamma-1 trials, late thrombosis rates of 5–7% were seen.

Treatment using Ir-192 for in-stent restenosis in high-risk lesions has also been shown to be efficacious. The Long WRIST trial for long in-stent restenosis lesions between 40–80 mm[14] and the SVG WRIST[15] have both reported marked advantages of γ-radiation in this particularly difficult subset.

The gamma trial results are summarised in table 1.

Beta-radiation trials

The BERT trial investigated the use of the β-isotope strontium/yttrium-90 (Sr/Y-90) delivered via a non-centered blinding 5Fr catheter to reduce restenosis following coronary angioplasty.[16] The original trial was essentially a dose-finding registry with no control group. For the group as a whole the angiographic restenosis rate was 17% and there was a suggestion of a dose effect, with better results being achieved with higher radiation doses. This preliminary study showed that the

Table 1. Gamma intracoronary radiation restenosis trials

Trial	Results
SCRIPPS trial	Restenosis: 17% *vs*. 54% (p=0.01)
- 55 patients	TLR: 12% *vs*. 45% (p=0.01)
- Ir-192 *vs*. placebo, randomised trial	MACE: 15% *vs*. 48% (p=0.01)
γ-WRIST	Restenosis: 19% *vs*. 58% (p=0.0001)
- 130 patients	TLR: 13.8% *vs*. 63.1% (p=0.0001)
- Ir-192 *vs*. placebo, randomised trial	MACE: 29.2% *vs*. 67.7% (p=0.001)
GAMMA-1	Restenosis: 32% *vs*. 55% (p=0.01)
- 252 patients	TLR: 24.4% *vs*. 42.1% (p=0.01)
- Ir-192 *vs*. placebo, randomised trial	MACE: 28.2% *vs*. 43.8% (p=0.02)
Long WRIST	Restenosis: 32% *vs*. 71% (p=0.01)
- 120 patients	TLR: 30.0% *vs*. 60.0% (p=0.01)
- Ir-192 *vs*. placebo, randomised trial	MACE: 38.3% *vs*. 61.7% (p=0.01)
SVG WRIST	Restenosis 21% *vs*. 45% (p=0.005)
- 120 patients	TLR: 10% *vs*. 48.3% (p<0.001)
- Ir-192 *vs*. placebo, randomised trial	MACE: 20% *vs*. 55% (p<0.001)

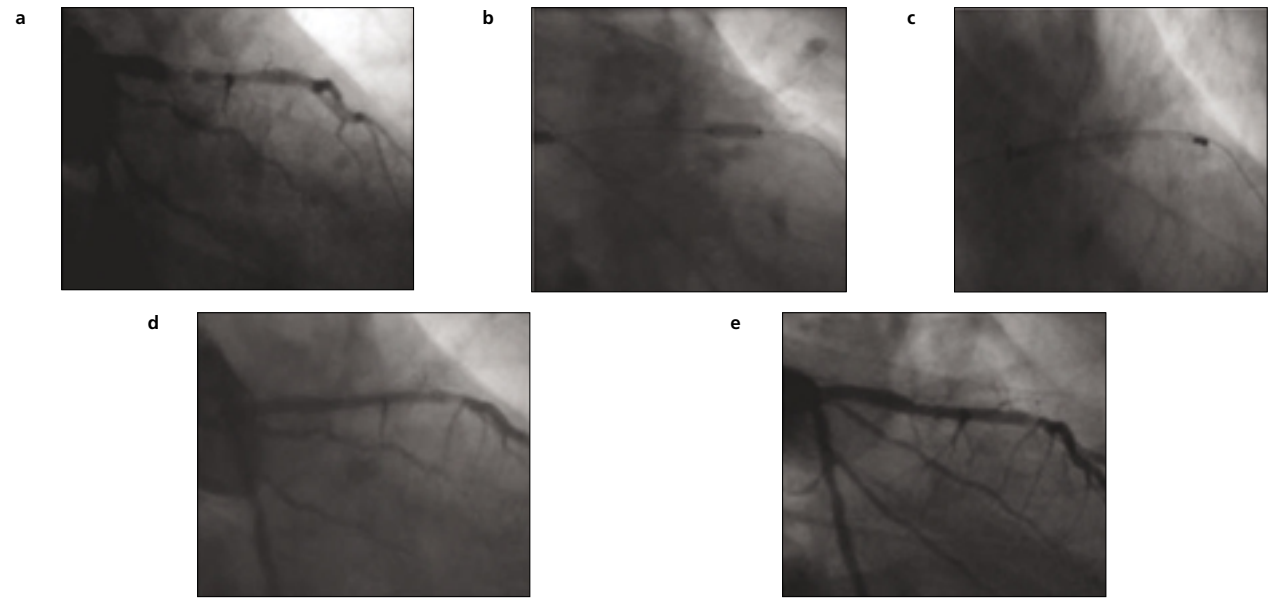
Key: restenosis = angiographic restenosis; TLR = target lesion restenosis; MACE = major adverse cardiac events (death, Q-wave myocardial infarction or target vessel revascularisation)

Table 2. Beta intracoronary radiation restenosis trials

Trial	Results
β-WRIST	Restenosis: 34% *vs*. 71.1% (p=0.001)
- 60 patients	TLR: 28% *vs*. 66% (p=0.001)
- Y-90 registry compared to β-WRIST placebo arm	MACE: 34% *vs*. 76% (p=0.001)
START	Restenosis: 28.8% *vs*. 45.2% (p=0.001)
- 479 patients	TLR: 13.1% *vs*. 22.4% (p=0.008)
- Sr/Y-90 *vs*. placebo, randomised trial	MACE: 18% *vs*. 25.9% (p=0.03)
INHIBIT	Restenosis: 26% *vs*. 52% (p=0.003)
- 132 patients	TLR: 11% *vs*. 29% (p=0.001)
- P-32 *vs*. placebo, randomised trial	MACE: 22% *vs*. 33% (p=0.04)
START 40	Restenosis: 25.3% *vs*. 45.2% (p=0.001)
- 207 patients	TLR: 11.1% *vs*. 22.4% (p=0.002)
- Sr/Y-90 *vs*. registry compared to START placebo arm	MACE: 19.3% *vs*. 25.9% (p=0.01)

Key: Restenosis = angiographic restenosis; TLR = target lesion restenosis; MACE = major adverse cardiac events (death, Q-wave myocardial infarction or target vessel revascularisation)

Figure 1. **a**) Diffuse in-stent restenosis four months following stent deployment in the left anterior descending coronary artery; **b**) balloon angioplasty using 3.5/10 mm cutting balloon; **c**) intracoronary brachytherapy with Sr/Y-90, delivered via Novoste Beta-Cath catheter; **d**) final angiographic result; **e**) six-month angiographic follow-up showing no evidence of restenosis



use of β-radiation was safe, and was the catalyst for further studies for both in-stent restenosis and *de novo* lesions.

Beta in-stent restenosis trials

Beta WRIST demonstrated similar results to the original WRIST trials, this time using β-radiation to treat in-stent restenosis using yttrium-90 (Y-90) source in a non-randomised registry.[17] Subsequently, two major multicentre placebo-controlled studies using radiation to treat in-stent restenosis have reported. Both the START[18] and INHIBIT[19] trials reported a marked reduction in both angiographic and clinical event rates when β-radiation was compared to placebo in the treatment of in-stent restenosis (see table 2 and figure 1). Therefore a mandate is currently available for the use of both β- and γ-radiation for the clinical treatment of in-stent restenosis.

Data for the use of intracoronary radiation therapy for the treatment of *de novo* coronary lesions are less strong and still in development. The Dose-Ranging Trial, which was not placebo-controlled, did suggest a marked dose-dependent effect, with a remarkably low 4% angiographic restenosis rate in *de novo* non-stented coronary lesions receiving an 18Gy radiation dose.[20] Only one randomised placebo-controlled trial exists in this setting. The Beta Cath trial was a randomised trial for *de novo* lesions using the Sr/Y-90 source versus placebo.[21] The trial was initially designed in July 1997, at a time when there was only limited experience with intracoronary brachytherapy. Two potential complications of radiation therapy (stent thrombosis and geographic miss) dominated the results of the trial and no major advantages of radiation therapy were seen.[21] Perhaps the main message of this trial is the need for the full learning curve of a technique to be completed before embarking upon a major randomised trial.

Results of the beta in-stent restenosis trials are shown in table 2.

Potential complications of brachytherapy

Edge effect and geographical miss

A potential drawback of radiation treatment is the development of new lesions at both edges of the irradiated segment, the so-called 'edge effect'. Animal studies have shown a dose-dependent effect using intracoronary Ir-192 radiation prior to over-stretch injury in the pig model, with a stimulatory effect at 10 Gy and a marked reduction of neointima formation at >15 Gy.[23] The 'edge effect' involves the delivery of a low (potentially stimulatory) dose of radiation at the margins of an injured segment, resulting in excessive healing and a reduced luminal diameter at the margins of the original lesion. The term 'geographic miss' refers to a procedural event where an injured segment of artery is not covered ('missed') subsequently by the radiation device.[24,25]

There is some debate as to whether either of these conditions truly exists or whether the 'edge effect' merely displays a relocation of the minimal luminal diameter to the edge of the treatment site (which is often diseased) because of the marked radiation effect at the original lesion site. The technical problem of the edge effect is highlighted by the radioactive stent[26] which has an almost inevitable 'edge effect' because of the deployment balloon. Despite many attempts to solve the problem of the injury caused by the deployment balloon and low-dose radiation at the edges of the stent, restenosis rates with this device have remained high.[27]

Key messages

- Restenosis is the greatest challenge in interventional cardiology
- A mandate is available for use of both beta- and gamma-radiation in treating in-stent restenosis
- Prolonged combination antiplatelet therapy is useful in preventing late stent thrombosis
- The prime use of coated stents may be during the index procedure to prevent restenosis

The strategies that may decrease the frequency of the edge effect include:

– operators learning the importance of positioning the radiation source across the injured segment and ensuring that there is good overlap into non-injured segments;
– the introduction of longer source trains to ensure complete coverage and overlap of the injured segments by the radiation source.[28]

Late stent thrombosis

In the early intra-coronary brachytherapy trials, despite 2–4 weeks of combination antiplatelet therapy, the incidence of late stent thrombosis (occurring 4–7 months after the procedure) was reported to be up to 9.1% in patients who received brachytherapy for in-stent restenosis, compared to 1.2% in the placebo group. There was no difference between γ- or β-isotopes.[29] All the earlier trials appeared to indicate that the increased rate of late occlusions appeared to be due to the combination of re-stenting, radiation and short-term antiplatelet therapy. It has been hypothesised that late thrombosis is caused by the pronounced delay in stent endothelialisation that occurs after exposure to radiation.

In the Beta Cath trial, patients in the original stent arm, who received radiation and 2–4 weeks of combination antiplatelet therapy, had a 6.8% incidence of late stent thrombosis. This problem was solved with the addition of a new stent arm with prolonged combination antiplatelet therapy for longer than 60 days: in this arm the incidence of late thrombosis fell to that of the placebo group (1.3% vs. 0.8%).[21] These results were also confirmed by other more recent trials where prolonged antiplatelet therapy was used.[18,19,30] Multivariate analysis has shown that new stent implantation performed at the time of the radiation procedure was the main predictor of late stent thrombosis.[29] In summary, the incidence of late stent thrombosis appears to have been resolved by the use of prolonged combination antiplatelet therapy, and the avoidance when possible of repeat stenting at the time of the radiation procedure.

Possible long-term complications

The longest follow-up of any patient who has undergone intra-coronary brachytherapy is approaching six years. There are clear worries about potential long-term complications of this procedure. These include:

- late fibrosis leading to 'delayed' restenosis;
- late 'thinning' of the vessel wall leading to aneurysm formation; and
- 'new' tumour formation either at a local or distant site.

None of these complications has been seen in patients so far but continued vigilance is clearly necessary.

Future role for brachytherapy

The local administration of medications to the site of vascular injury by using polymer-coated stents appears a rational approach to the prevention of in-stent restenosis. The use of the potent immunosuppressive agent, sirolimus, in a coated stent has shown promising preliminary results, with only minimal neointimal proliferation seen at four months, and no major clinical events up to eight months.[31] However, the indications for coated stents appear to be different, with their prime use during the index procedure to prevent restenosis. The role of these devices in the treatment of in-stent restenosis remains to be assessed.

Further studies are still required to assess the use of intracoronary radiation for complex *de novo* lesions with higher restenosis rates such as long lesions, diabetic vessels, saphenous vein grafts and small vessels. It is unlikely that intracoronary brachytherapy will be delivered twice to the same site and this may play an important part in the decision-making process. By contrast, intracoronary brachytherapy has a proven place in the treatment of in-stent restenosis and, until efficacy is shown with polymer-coated stents for in-stent restenosis, intracoronary brachytherapy will remain the gold standard treatment for this condition.

References

1. Bergelson BA, Fishman RF, Tommaso CL. Abrupt vessel closure: changing importance, management, and consequences. *Am Heart J* 1997;**134**(3):362-81.
2. Serruys PW, de Jaegere P, Kiemeneij F *et al*. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. BENESTENT study group. *N Engl J Med* 1994; **331**:449-95.
3. Moussa I, Di Mario C, Moses J *et al*. Comparison of angiographic and clinical outcome of coronary stenting of chronic total occlusions versus sub-total occlusions. *Am J Cardiol* 1998;**81**:1-6.
4. Baim DS, Levine MJ, Leon MB, Levine S, Ellis SG, Schatz RA. Management of restenosis within the Palmaz-Schatz coronary stent (The US Multicenter Experience). *Am J Cardiol* 1993;**71**:364-6.
5. Van den Brenk HAS, Minty CC. Radiation in the management of keloids and hypertrophic scar. *Br J Surg* 1959/60;**47**:595-605.
6. Scott NA, Cipolla GD, Ross CE *et al*. Identification of a potential role for the adventitia in vascular lesion formation after balloon overstretch injury of porcine coronary arteries. *Circulation* 1996;**93**:2178-87.
7. Waksman R, Robinson KA, Crocker IR *et al*. Endovascular low-dose irradiation inhibits neointima formation after coronary artery balloon injury in swine. A possible role for radiation therapy in restenosis prevention. *Circulation* 1995;**91**:1533-9.
8. Verin V, Popowski Y, Urban P *et al*. Intra-arterial beta irradiation prevents neointimal hyperplasia in a hypercholesterolemic rabbit restenosis model. *Circulation* 1995;**92**:2284-90.
9. Verin V, Urban P, Popowski Y *et al*. Feasibility of intra-coronary beta-irra-

diation to reduce restenosis after balloon angioplasty: A clinical pilot study. *Circulation* 1997;**95**:1138-44.
10. Condado JA, Waksman R, Gurdiel O *et al*. Long-term angiographic and clinical outcome after percutaneous transluminal coronary angioplasty and intracoronary radiation therapy in humans. *Circulation* 1997; **96**(3):727-32.
11. Teirstein PS, Massullo V, Jani S *et al*. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med* 1997;**336**:1697-703.
12. Waksman R, White L, Chan RC *et al.* Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. *Circulation* 2000;**101**(18):2165-71.
13. Leon NB, Teirstein PS, Moses JW *et al*. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med* 2001;**344**(4):251-6.
14. Waksman R. Washington Radiation for In-Stent Restenosis Trial for Long Lesions (Long WRIST). 49th Scientific Session of the American College Cardiology, Anaheim, CA, 2000.
15. Waksman R. Washington Radiation for In-Stent Restenosis Trial for Saphenous Vein Grafts (SVG WRIST). 50th Scientific Session of the American College of Cardiology, Orlando, FL, 2001.
16. King SB 3rd, Williams DO, Chougule P *et al*. Endovascular beta-radiation to reduce restenosis after coronary balloon angioplasty: results of the beta energy restenosis trial (BERT). *Circulation* 1998;**97**(20):2025-30.
17. Waksman R, Bhargava B, White L *et al*. Intracoronary beta-radiation therapy inhibits recurrence of in-stent restenosis. *Circulation* 2000;**101**:1895-8.
18. Popma J. Stents and radiation trial (START). 49th Scientific Session of the American College of Cardiology, Anaheim, CA, 2000.
19. Waksman R. INHIBIT trial (Beta radiation to inhibit recurrence of in-stent restenosis). Clinical and angiographic results of the multicenter, randomised, double-blind study. *Circulation* 2000;**102**:9046.
20. Verin V, Popowski Y, de Bruyne B *et al*. Endoluminal beta-radiation therapy for the prevention of coronary restenosis after balloon angioplasty. *N Engl J Med* 2001;**344**(4):243-50.
21. Kuntz R. The De-Novo Beta Cath Trial. 50th Scientific Session of the American College of Cardiology, Orlando, FL, 2001.
22. Raizner AE, Oesterle SN, Waksman R *et al*. Inhibition of restenosis with beta-emitting radiotherapy: Report of the Proliferation Reduction with Vascular Energy Trial (PREVENT). *Circulation* 2000;**102**:951-8.
23. Weinberger J, Amols H, Ennis RD, Schwartz A, Wiedermann J, Marboe C. Intracoronary irradiation: dose response for the prevention of restenosis in swine. *Int J Radiol Oncol Biol Phys* 1996;**36**:767-75.
24. Sabete M, Costa MA, Kozuma K *et al*. Geographic miss. A cause of treatment failure in radio-oncology applied to intracoronary radiation therapy. *Circulation* 2000;**101**:2467-71.
25. Kim H, Waksman R, Cottin Y *et al.* Edge stenosis and geographical miss following intracoronary gamma radiation therapy for in-stent restenosis. *J Am Coll Cardiol* 2001;**37**:1026-30.
26. Albiero R, Adamian M, Kobayashi N *et al*. Short and intermediate term results of 32P radioactive-emitting stent implanation in patients with coronary artery disease: the Milan dose-response study. *Circulation* 2000;**101**:18-26.
27. Alberio R, Nishida T, Adamian M *et al*. Edge restenosis after implantation of high activity 32P radioactive β-emitting stents. *Circulation* 2000;**101**:2454-7.
28. Lansky A, Desai K, Constantino C *et al.* Predictors of stent and stent-edge restenosis after Sr/Y-90 radiation in the START 40 trial. *J Am Coll Cardiol* 2001;**37**:1A-648A.
29. Waksman R, Bhargava Balham, Mintz GS *et al.* Late total occlusion after intracoronary brachytherapy for patients with in-stent restenosis. *J Am Coll Cardiol* 2000;**36**:65-8.
30. Waksman R, Ajani AE, White RL *et al*. Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary gamma-radiation in patients with in-stent restenosis-Washington radiation for in-stent restenosis trial plus 6 months of clopidogrel (WRIST PLUS). *Circulation* 2001;**103**:2332-5.
31. Sousa JE, Costa MA, Abizaid A *et al.* Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries. A quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation* 2001;**103**:192-5.