IN-STENT RESTENOSIS (ISR): THE PROBLEM AND POSSIBLE SOLUTIONS

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SUMMARY

This review article is focused on instent restenosis (ISR); its pathogenesis and different modalities tried for the treatment of this challenging problem. The dream of an effective treatment for ISR has eluded decades of effort by an army of investigators. No matter how much skill, experience, time, and effort the interventionist brings to the table, ISR can entirely reverse a perfect procedural result within months. Until now many strategies like conventional balloon angioplasty, perfusion balloon angioplasty (prolonged inflation), debulking of the lesion prior to balloon angioplasty using rotational or directional atherectomy, stent within stent implantation and treatment with Laser have all been tried but non has proved to be a fully effective solution to the problem or non has proved to be significantly superior to the other. However the efficacy provided by vascular brachytherapy and antiproliferative effect of the drug eluting stents has offered a hope to patients with in-stent restenosis

Keywords: -

INTRODUCTION

The pathogenesis of restenosis following conventional balloon angioplasty (CBA) can be divided into four phases:

1. Early elastic recoil- hours to days.
2. Mural thrombus formation - hours to days.
3. Neointimal proliferation and extracellular matrix formation – weeks.
4. Chronic geometric arterial changes (re-modelling) - months.

Two randomized trials of intravascular stenting versus balloon angioplasty alone {Benestent[1], and STRESS[2]} have shown that stents decrease restenosis, and this is thought to be due to their preventing early elastic recoil and late arterial re-modelling[3,4]. Mural thrombus formation together with neointimal proliferation and extra cellular matrix formation can still, however, lead to restenosis at the stent site.

Incidence of in-stent restenosis (ISR)

This varies from 6% up to 40% depending on:

1. Type of stent used
2. Indication for stent placement (bailout, Primary PTCA, sub-optimal PTCA result, elective)
3. Type, location, and length of the lesion stented, and native coronary artery or saphenous vein graft
4. High or low pressure used to deploy the stent
5. Post-stent anti-platelet / anti-coagulant regime
6. Clinical and / or angiographic criteria used to define restenosis.

Early experience (1986-1993) at the CHUV Lausanne[5,6], using Wall stents (WaS), Palmaz-Schatz stents (PSS), and Wiktor stents (WiS), showed an overall early closure rate of 14.4%, and an overall late clinical restenosis rate of 19.2% in 243 consecutive successful stent procedures.

Both for Gianturco-Roubin(GRS) stents[7], and for PSS[8] there is angiographic evidence that significant late regression of ISR can occur, which can sometimes be dramatic, so that patients with a stable clinical course and angiographic ISR may often be treated medically rather than routinely redilated. One year clinical follow-up of the Benestent trial patients[9] showed no significant differences in mortality (1.2 vs 0.8%), stroke (0 vs 0.8%), MI (5.0 vs 4.2%), or

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CABG (6.9 vs 5.1 %) between the stent and PTCA groups respectively. However, the need for re-PTCA was significantly lower in the stent group (10%) than the PTCA group (21%, p=.001). In the Benestent-II Pilot study[10], the subgroup of patients treated with stents coated with polyamine and end-point-attached heparin and given aspirin and ticlopidine as anti-platelet therapy after stenting had no early stent thrombosis, and an angiographic restenosis rate of 6%. This compares most favourably with reports of angiographic restenosis rates for the uncoated PSS that can be (at best) 18% for stenotic lesions[11], 20% in chronic total occlusions[12], and 28% for ostial lesions[13]. In an interesting presentation at the 1996 American College of Cardiology Meeting, Sawada gave the six-month angiographic follow-up data from the Kokura Memorial Hospital for 152 lesions that were comparable to those included in the STRESS and Benestent trials (SIB equiv), 236 small vessel lesions (ref. diam. <3.0mm), 125 long lesions (> 15mm long), 97 ostial lesions, 40 total occlusions, 52 vein graft lesions, 301 restenotic lesions, and 96 lesions with poor LV function[14]. The restenosis rate in this series thus varied from 11 to 40%, and the need for TLR from 7.5 to 21 % depending on the type of lesion. ISR may also be more severe in diabetic patients[15]. Different types of stent have different patterns of restenosis. With the PSS, focal restenosis is more common than diffuse restenosis, and occurs at the articulation site and at the ends of the stent[11,15].

TREATMENT

Treatment options include:

1. Conventional balloon angioplasty.
2. Perfusion balloon angioplasty (prolonged inflation).
3. Debulking of the lesion prior to balloon angioplasty using a) Rotational atherectomy (RA) using Rotablator , b)Laser, c) Directional atherectomy, d) Transluminal Extraction catheter (TEC)
4. Stent within stent implantation
5. Conservative medical management
6. Bypass surgery

1. Conventional balloon angioplasty (CBA).

Early reports have shown that treatment of ISR by CBA has a high initial success rate and a low complication rate, but recurrent angiographic restenosis was found in 31-57%[16-22]. In a multicenter Canadian study[23], angiographic restenosis (>50% diameter stenosis) occurred in 36/114 (32%) consecutive patients undergoing PSS implantation for elective or bailout indications. 31 of the 36 (86%) underwent repeat CBA with no immediate adverse events. Over a mean follow-up period of 43 to 22 months, target vessel revascularization was needed in 8 patients. 5 other patients required PTCA to a non-target artery, 3 patients (8%) suffered an MI in a non-target vessels territory, 2 patients (6%) had strokes, 1 patient died of lung cancer. Overall 20 of the 36 ISR patients (56%) were free from any cardiovascular event during follow-up.

From these reports we can conclude that:

a) CBA for ISR is safe and effective in the short term.

b) CBA for ISR results in a further restenosis in a substantial proportion of cases.

c) Progression of disease in non-target vessels is an important additional factor reducing event-free survival.

d) There is a need for new strategies to manage this challenging patient population.

2. Perfusion balloon angioplasty.

There are no reports in the literature to suggest that prolonged balloon inflation using a perfusion balloon is any more effective than CBA.

3. Debulking.

a) Rotational atherectomy (RA)

Rotablator. The use of RA to debulk ISR prior to low-pressure balloon inflation was first described in a case report by Stone[24]. He suggested that it would seem inherently desirable (though unproven) not to abrade the stent struts with the high-speed rotating diamond tipped burr. Intravascular ultrasound (IVUS), by determining eccentricity of the in-stent lumen and by accurately measuring the stent

diameter, might therefore add safety to the procedure and aid accurate burr sizing. The largest single centre experience is probably that of Mount Sinai Hospital in New York[25]. They have treated 38 cases with no major complications and 100% procedural success. Mean burr/stent ratio was 0.55 in the first 7 cases, and >0.7 in subsequent cases. The final average burr size was 2 mm and in all cases RA was followed by CBA using low inflation pressures (4 to 5 bar). Stent area was unchanged. 67% of the cases have now been followed up for more than 4 months, and there have been 10 recurrences of ISR (26%) - 3 treated by CABG (1 death), 6 by repeat percutaneous intervention, and 1 by continued medical therapy.

The results of a 10 centre registry containing 50 lesions with ISR in 45 patients has been presented[26]. The majority were PSS (45 lesions), and the mean time from implantation 6 months. A mean of 2.3 burrs were used per lesion with a burr/artery ratio of 0.72, and adjunctive CBA was used in 65%. IVUS was used in 35%. 2 patients required additional stents for distal dissection without clinical sequelae.

b) Laser.

The largest single centre experience comes from the Eppendorf University Clinic in Hamburg (Prof. CW Hamm) with 41 cases[27], also with a low complication rate (2 nQMI, 1 rePTCA, 1 dissection, and 1 distal embolus - the cause of 1 of the nQMI). Of interest was the Hamburg IVUS finding that in 10 of 23 patients (43%), the stent was not fully deployed. This is in keeping the observations that after angiographicaIly successful stent deployment (using balloon pressures in the 8 to 16 bar range), IVUS shows that under half of the stents are fully deployed (6/21 PSS, 3/12 AVE, 0/5 WiS). Restenosis rates following ELCA debulking of ISR are not promising.

c) Directional coronary atherectomy (DCA).

Strauss et al.[28] described 9 patients undergoing 10 DCA procedures for ISR. Restenosis requiring re-intervention occurred after 4 procedures (40%). DCA resulted in the disruption of a WiS in 1 patient. Disruption of a Flex Coil Cook stent (GRS) by DCA was reported[29]. Hence DCA cannot at present be widely recommended for the treatment of ISR.

d) Transluminal extraction catheter (TEC).

TEC has been used in 2 patients to debulk ISR prior to CBA[30], but this device is not widely used, and is unlikely to become a first choice treatment.

4. Stent within stent implantation.

This is a logical treatment strategy under the following conditions:

a) The previously implanted stent provides insufficient radial force to overcome elastic recoil and hold the artery lumen widely open.

b) There is evidence of inward prolapse of tissue between the stent struts.

Both are more likely to be encountered in wire coil open mesh stents than in slotted tube stents. It is not a good option where the first stent has not been fully deployed. Drug eluting stent may a better choice where hyperplasia is the dominant feature (see below).

5. Brachytherapy.

Brachy from the Greek word brakhus meaning short, referring to the short distance between the source{intravascular source} and target cells, is now available for the treatment of instent restenosis. Currently the radiation is delivered via the catheters containing radioactive wires or pellets. Other devices under investigation include radioactive stents , a beta emitting liquid filling balloon, or a balloon coated with a beta emitting source. In direct comparison of brachytherapy and routine PCI (balloon angioplasty with or without atherectomy), for the treatment of instent restenosis , intracoronary irradiation reduces the incidences of restenosis by 50%[31-36]

6 Medical Treatment.

Reference has already been made to the possibility of late regression of ISR[7,8], so that there are sound reasons for deferring further intervention as long as the patient is stable, and symptoms are not too disabling.

7. Bypass surgery (CABG).

The treatment of ISR by percutaneous interventions carries a very low immediate risk, but the late results are disappointing with a very high incidence of repeat

ISR. CABG on the other hand has an obviously greater immediate risk but a far lower need for further intervention in the medium term. There are no randornised trials comparing percutaneous interventions with CABG in the treatment of ISR, and decisions, therefore, can only be made on the basis of physician and patient preference, co-morbid conditions (if present), location of the lesion, whether the patient has had previous CABG, access to medical care and follow-up, and available skills and facilities.

PREVENTION

Current:

Ensure that all stents are fully deployed; by correct sizing, by high-pressure balloon inflation at the time of deployment and by having a low threshold for the use of IVUS (if available). Use of aspirin and antiplatelets unless contraindicated, if possible starting the clopedogril/ticlopidine 48 hours before the procedure.

Heparin coated stents have been tried but proved to be unsuccessful. Drug eluting stents are now becoming popular with long term favourable results and should be deployed in the first instance especially at the vulnerable sites like small vessels in diabetics, osteal, bifurcation, long and diffuse lesions.

FUTURE:

1. Local drug delivery-Drug Eluting Stents

Pre-eminent among new devices is the drug eluting (coated) stent, which acts as a drug delivery device to reduce restenosis. The first of these was the sirolimus coated Cypher stent. Sirolimus is one of several agents that have powerful antimitotic effects and inhibit new tissue growth inside the artery and stent. In a randomised controlled trial (RAVEL) this stent gave a six-month restenosis rate of 0% compared with 27% for an uncoated stent of the same design (Bx Velocity). A later randomised study (SIRIUS) of more complex lesions prone to restenosis still produced a low rate of restenosis within stented segments (9% v 36% with uncoated stents), even in patients with diabetes (18% v 51% respectively). Other randomised studies such as ASPECT and TAXUS II have also shown that coated stents (with the cytotoxic agent paclitaxel) have significantly lower six month restenosis rates than identical uncoated stents (14% v 39% and 6% v 20% respectively). By reducing the incidence of restenosis (and therefore recurrent symptoms), drug eluting stents will probably alter the balance of treating coronary artery disease in favour of percutaneous intervention rather than coronary artery bypass surgery.

The use of special balloons or stent delivery systems has attracted much attention, and agents that have been suggested or tried include: heparin, low-molecular-weight heparin, prednisolone, GP IIb/IIIa inhibitors (MK-383-Aggrastat; Reopro), Globulin, the gene encoding vascular endothelial growth factor (VEGF), Nitroglycerin. The results have not been promising apart from drug eluting stents as mentioned above

2. Better stent design.

Efforts are also underway to improve the material and designs of bare mettle stents that should yield the results similar to the drug eluting stents in terms of reducing late luminal loss.

3. Better platelet inhibition.

a) Glycoprotein IIb/IIIa inhibitors (“Reopro”, “Integrilin”, “Tirofiban”) have been shown to reduce MACE events and restenosis especially in diabetics if administered before or during the stent procedures[37].

b) Cilostazol, a potent antiplatelet drug which increases the intracellular cyclic AMP concentration both in platelets and vascular smooth muscle cells has, in a randomized trial, been shown to reduce significantly late lumen loss compared to aspirin following PSS implantation[38].

4. Antiproliferative agents.

Trapidil inhibits thromboxane A2 and is a competitive PDGF receptor antgagonist. In the ST ARC trial, 354 patients were assigned to trapidil 100 mg three times daily or aspirin starting at least 3 days before PTCA and continued for 6 months. The restenosis rate was 26% in the trapidil group compared to 44% with aspirin, and the trapidil group also had less unstable angina (18 % vs 31 %)[39].

5. Somatostatin analogues.

Angiopeptin (a cyclic octopeptide) inhibits IGF-1 and fibroblast growth factor, and has been shown to reduce the clinical event rate (mainly TLR - 28% vs 36%) at 12-month follow-up after PTCA in a randomized double- blind placebo controlled trial of 553 patients. It did not significantly lower the angiographic restenosis rate[40].

6. Anti-keloid drugs.

Tranilast, an anti-allergic anti-keloid drug, in a dose of 600mg/day started the day after the procedure was tested against placebo in a subgroup of the TREAT (Tranilast Restenosis following Angioplasty Trial) study, who received stents at the time of their index PTCA. Follow-up angiography was performed at 3 and 6 months and in this small study the patients who received Tranilast showed significant reduction in restenosis[41].

7. Drugs preventing LDL oxidation.

The Probucol Angioplasty Restenosis Trial (PART) randomly assigned 101 patients to probucol 1000 mg daily starting 4 weeks prior to PTCA and continuing until angiographic restudy 24 weeks post-PTCA) or control (no lipid lowering drug administered). All patients were followed for 1 year after PTCA for death, acute MI, and TLR There was no significant reduction in restenosis although reduction in mortality was observed in Probucol group[42,43].

Intensive LDL-cholesterol lowering with lovastatin after PTCA also failed to influence restenosis(44), but a meta-analysis of the many small trials of treatment with various doses of omega-3 fatty acids (fish oil) has shown significant reduction of clinical and angiographic end-points for restenosis[45]. The results of large-scale trials are awaited.

8. Gene therapy.

For a review please see reference [46].

CONCLUDING REMARKS

ISR is currently a difficult problem to handle. Scores of devices, number of drugs, and innumerable revascularization “strategies” have failed to eliminate the 10% to 40% risk of recurrence after coronary stenting. Prevention of restenosis is therefore the best strategy to remember. We are not sure whether we are overdoing in terms of using more and more stents and leaving the traditional practice of balloon PTCA altogether especially in type A lesions if stent like results are achieved with ballooning alone. However in situations like osteal lesions, true bifurcations, proximal LAD, total occlusions and smaller vessels in diabetics, the best strategy may be to deploy a drug eluting stent if cost is not the issue. Although in the current and future era the data strongly support the use of drug eluting stents in almost all situations but in our circumstances where cost is a major issue, use of bare mettle stents especially in larger vessels may still be a better choice. Use of II b IIIa receptor blockers especially during stenting in diabetics and in ACS or primary PTCA may significantly reduce the incidence of restenosis. However once the ISR is established the scope of long term effective treatment is limited and is yet to be found. In this situation if CBA is ineffective brachytherapy although is a better choice but is practically difficult and costly in our country. Use of drug eluting stent within stent offers a better hope but needs to be further evaluated.

REFERENCES

1. Serruys PW, de Jaegere P, Kieemeneij F, et al: A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Eng J Med 1994 331 :489-95

2. Fischman DL. Leon MB, Bairn DS, et al: A randomised comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994 331 :496-50 1.

3. Dangas G, Fuster V: Management of restenosis after coronary intervention. Am Heart J 1996 132:428-36.

4. Mintz GS, Popma JJ, Hong MK, Pichard AD, et al: Intravascular ultrasound to discern device-specific effects and mechanisms of restenosis. Am J Cardiol1996 78:18-22.

5. Eeckhoute E, van Melle G, Stauffer JC, et al: Can early closure and restenosis after endolurninal stenting be predicted from clinical, procedural

and angiographic variables at the time of intervention? Br Heart J 1995 74:592-7

6. Klugherz BD; DeAngelo DL, Kim BK, et al: Three-year clinical follow-up after Palmaz-Schatz stenting. J Am ColI Cardiol1996 27:1185-91

7. Hermiller JB, Fry ET, Peters TF, et al.: Late coronary artery stenosis regression within the Gianturco-Roubin intracoronary stent. Am J Cardiol1996 77:247-51

8. Kimura T, Yokoi H. Nakagawa Y, et al. Three-year follow-up after implantation of metallic coronary-artery stents. N Engl J Med 1996 334:561-6

9. Macaya C, Serruys PW, Ruygrok P, et al.: Continued benefit of coronary stenting versus balloon angioplasty: one-year clinical follow-up of Benestent trial. Benestent Study Group. J Am ColI Carrdiol 1996 27:255-61

10. Serruys PW, Emanuelsson H, Van der Giessen W, et al.: Heparin coated Palmaz-Schatz stents in human coronary arteries. Early outcome of the Benestent-II Pilot Study. Circulation 199693:412-22

11. Ikara Y, Hara K, Tamura T, et al.: Luminal loss and site of restenosis after Palmaz-Schatz coronary stent implantation. Am J Cardiol1995 76: 117-20.

12. Goldberg SL, Colombo A, Borrione M, et al.: Intracoronary stent insertion after balloon angioplasty of chronic total occlusions. J Am ColI Cardiol 1995 26:713-9.

13. Rocha-Singh K, Morris N, Wong SC, Schatz RA, Teirstein PS: Coronary stenting for treatment of ostial stenoses of native coronary arteries or aorto-coronary saphenous vein grafts. Am J Cardiol 199575:26-9.

14. Sawada Y, Nosaka H, Kimura T, Nobuyoshi N: Initial and six months outcome of Palmaz-Schatz stent implantation: STRESS/Benestent equivalent Vs non-equivalent lesions (abstract). J Am ColI Cardiol 1996 27:252A

15. Carozza P, Kuntz RE, Fishman RF, Bairn DS: Restenosis after arterial injury caused bu coronary stenting in patients with diabetes mellitus. Ann Intern Med 1993 118:344-9.

16. Dussaillant GR, Mintz GS, Pichard AD, et al.: Small stent size and intimal hyperplasia contribute to restenosis: a volumetric intravascular ultrasound analysis. J Am ColI Cardiol1995 26:720-4.

17. Gordon PC, Gibson CM, Cohen DJ, et al.: Mechanisms of restenosis and redilatation within coronary stents - quantitative angiographic assessment. J Am ColI Cardiol 1993 21: 1166-74.

18. Bairn DS, Levine MJ, Leon ME, et aI.: Management of restenosis within the PaImaz-Schatz coronary stent (the US multicenter experience). Am J Cardiol1993 71:364-6.

19. Schmog A, Kastrati A, Dietz R, et al.: Emergency coronary stenting for dissection during percutaneous transluminaI coronary angioplasty: Angiographic follow-up after stenting and repeat angioplasty of the stented segment. J Am ColI Cardiol1994 23: 1053-60.

20. Macander PJ, Roubin GS, Agrawal SK, et al.: Balloon angioplasty for treatment of in-stent restenosis: Feasibility, safety and efficacy. Cathet Cardiovasc Diagn 199432: 125-31

21. Debbas N, Eeckhout E, Stauffer JC, et al: Traitement par angioplastie au ballonnet de restenoses survenues sur protheses endocoronaires. Arch Mal Coeur Vaiss 199588:987-91.

22. Tan R-C, Sketch MRJr, Tan ME, et al.: Is there an

optimal treatment strategy for stent restenosis? (abstract) Circulation 199694:1-91.

23. Sridhar K, Teefy PJ, Almond DG, et al.: Long-term clinical outcome of patientes with in-stent restenosis (abstract) Circulation 199694:1-454.

24. Stone GW: Rotational atherectomy for treatment of in-stent restenosis: Role of intracoronary ultrasound guidance. Cathet Cardiovasc Diagn 1996 Supplement 3:73-7.

25. Sharma SK, Duvvuri S, Kakarala V, Dangas G, et al.: Rotational atherectomy for in-stent restenosis: Intravascular ultrasound and quantitative coronary angiography (abstract) Circulation 199694:1-454.

26. Buchbinder M, Goldberg S, Fortuna R, et L: Rotational atherectomy for intra-stent restenosis: Initial experience. (abstract) Circulation 1996 94:1-621

27. Koster RP, Koschyk DR, Kahler J, et al.: Laser Angioplasty of in-stent restenosis. Circulation 199694:1-621.

28. Strauss BH, Omans VA, van Suylen RJ, et al.: Directional atherectomy for treatment of restenosis within coronary stents: Clinical angiographic and histologic results. J Am ColI Cardiol. 199220:1465-73.

29. Bowerman RE, Pinkerton CA, Kirk B, Waller BF: Disruption of a coronary stent during atherectomy for restenosis. Cather Cardiovasc Diagn 1991 24:248-51.

30. IkariY, Yamaguchi T, Tamura T, et al.: Transluminal extraction atherectomy and adjunctive balloon angioplasty for restenosis after PaImaz-Schatz coronary stent implantation. Cathet Cardiovasxc Diagn 1993 30:127-30.

31. Teirstein P, Masullo V, Jani s, et al.: Radiation therapy following stenting - 6 month follow-up of a randomized clinical trial. (abstract) Circulation 199694:1-210.

32. Wise J : Radiation may prevent restenosis (News) Brit Med J 1996 313: 1227

33. Urban P, Verin V, Popowski Y, et al.: Clinical feasibility and safety of intraluminal Beta irradiation to prevent restenosis after coronary balloon angioplasty. (abstract). Circulation 199694:1-210

34. Park SW , Hong MK. Treatment of diffuse instent restenosis with rotational atherctomy followed by radiation therapy J Am Coll Cardiology 2001;38;631-637

35. Raizner AE, Oesterle SN. Inhibition of restenosis with b Emiting radiotherapy. Circulation 2000.102;951-958

36. Leon MB, Teirsten PS. Localized intracoronary irradiation therapy to inhibit the recurrence of restenosis after stenting. N Eng J Med 2001; 344; 250-256

37. Topol EJ, Califf RM, Weisman HF, et al. on behalf of the EPIC Investigators: Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. Lancet 1994343:881-9.

38. Hara K, Yamasaki M, Kohzuma K, et aI.: Cilostazol reduces late lumen loss aftger the Palmaz-Schatz stent implantation (abstgract). Circulation 199694:1-91

39. Maresta A, Balducelli M, Cantini L, et al.: Trapidil (triazolopyrimidine), a platelet-derived growth factor antagonist, reduces restenosis afger percutaneous transluminal coronary angioplasty. Results of the randomizes double-blind STARC study. Circulation 199490:2710-5.

40. Emanuelsson H, Beatt KJ, Bagger JP, et al. for

the European Angiopeptin Study Group: Long-termeffects of angiopeptin treatment in coronary angioplasty. Reduction of clinical events but not angiographic restenosis. Circulation 1995 91: 1689-96.

41. Hsu Y-S, Tarnai H, Veda K, et al.: Efficacy of tranilast after coronary stenting (abstract). Circulation 1996 94:1-620.

42. Yokoi H, Kuwabara Y, Yamaguchi H, The PART Group: One-year follow-up results of the Probucol Angioplasty Restenosis Trial (PART) (abstract). Circulation 199694:1-91.

43. Tardif J-C, Cote G, Lesperance J, et al.: Prevention of restenosis by ore and post PTCA probucol therapy. A randomized clinical trial. (Abstract). Circulation 199694:1-91.

44. Weintraub WS, Boccuzzi 5J, Klein JL, et aI., and the Lovastatin Restenosis Trial Study Group: Lack of effect of lovastatin on restenosis after coronary angioplasty. N Engl J Med 1994 331: 1331- 7.

45. Hillegass WB, Ohman EM, Califf RM: Restenosis: the clinical issues. In: Topol EJ editor. Textbook of Interventional Cardiology, 2nd. ed. Philadelphia: WB Saunders, 1994415-35.

46. Dangas G, Fuster V: Management of restenosis after coronary intervention. Amer Heart J 1996 132:428-36.

39. Hillegass WB, Ohman EM, Califf RM: Restenosis: the clinical issues. In: Topol EJ editor. Textbook of Interventional Cardiology, 2nd. ed. Philadelphia: WB Saunders, 1994415-35.

40. Dangas G, Fuster V: Management of restenosis after coronary intervention. Amer Heart J 1996 132:428-36.

41. Teirstein P, Masullo V, Jani s, et al.: Radiation therapy following stenting - 6 month follow-up of a randomized clinical trial. (abstract) Circulation 199694:1-210.

42. Wise J : Radiation may prevent restenosis (News) Brit Med J 1996 313: 1227

43. Urban P, Verin V, Popowski Y, et al.: Clinical feasibility and safety of intraluminal Beta irradiation to prevent restenosis after coronary balloon angioplasty. (abstract). Circulation 199694:1-210

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