

Intracoronary Radiation Therapy

An Evidence-Based Analysis

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Contact Information

The Medical Advisory Secretariat
Ministry of Health and Long-Term Care
20 Dundas Street West, 10th floor
Toronto, Ontario
CANADA
M5G 2N6
Email: MASinfo.moh@ontario.ca
Telephone: 416-314-1092

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GLOSSARY

Binary or dichotomy restenosis rate	The percentage of patients in whom there is a recurrence of $\geq 50\%$ of diameter stenosis in the target lesion as determined by angiography
Target lesion	The stented segment in addition to the stent margins 5 mm proximal and distal to the radioactive or placebo sources.
Target-lesion revascularization	Balloon dilatation or surgical bypass of the target vessel due to the presence of $\geq 50\%$ of diameter stenosis of the target lesion as measured by angiography. Target lesion revascularization includes revascularization of both in-stent stenosis and stenosis at the stent or source margins.
Target – vessel revascularization	Includes revascularization of the target lesion or a segment outside the target lesion but within the same vessel.
Non-target vessel revascularization	Revascularization of an epicardial vessel that did not contain the target lesion.
MACE	Major adverse cardiac event

OBJECTIVE

The objective of this health technology policy assessment was to determine the effectiveness and cost-effectiveness of intracoronary radiation in preventing in-stent restenosis.

BACKGROUND

Clinical Need

Coronary artery disease is a major cause of mortality and morbidity. Clinical effects include stable or unstable angina and acute manifestations such as myocardial infarction [MI]. Treatments include control of risk factors, drug therapy, coronary bypass graft surgery [CABG] and percutaneous coronary interventions [PCI] including balloon dilatation and stenting.[1]

Studies and meta-analyses comparing CABG and balloon dilatation have shown no significant difference in mortality at six months for the two procedures, but showed a higher incidence of angina and higher revascularization rate for balloon dilatation (31%) than CABG (11%).[1] Despite these findings, balloon dilatation has become the preferred treatment for coronary artery stenosis because it is less invasive than CABG. More than 500,000 such procedures are performed each year in North America.

The major disadvantages of balloon dilatation are acute closure of the vessel during the procedure (2 - 10% of patients) and restenosis. Restenosis occurs in 30-40 % of patients within six months of balloon dilatation, requiring a second attempt in revascularization in the majority of cases.[2], [34] It has been recognized that negative arterial remodeling (circumferential constriction of the vessel wall), and neointimal hyperplasia (smooth muscle cell proliferation) in response to mechanical injury to the vessel wall, are the two main contributing factors to coronary restenosis.[3]

Coronary artery stents are metal tubes in the form of coils or expandable mesh that are inserted into coronary arteries via a catheter to widen the artery and increase blood flow. The insertion of a stent that acts as a scaffold after balloon dilatation has been shown to reduce the restenosis rate to 20-30%, primarily by eliminating negative remodeling.[34]

A 1996 survey by the Cardiac Care Network of Ontario [CCN] indicated that approximately 70% of patients receiving coronary stents do so for either restenosis prevention in favourable lesions, unfavourable anatomy with increased risk of acute complications, and/or stenosis and suboptimal result following balloon dilatation.[4] The Expert Panel on Intracoronary Stents of the CCN recommended, in a 1997 report, that funding be provided for the use of coronary stents in patients with specific conditions[4] and projected the use of stents in 55% of all interventional procedures. For the fiscal year of 2001-2002, the Ontario Government committed funding for approximately 11,000 stents (round off figure).

However, stenting cannot limit intimal hyperplasia. Excessive intimal hyperplasia results in in-stent stenosis. This poses another challenge because restenosis occurs in as many as 60% of patients who have been treated for in-stent stenosis.[2]

The Technology – Intracoronary Radiation Therapy

Intra-coronary radiation aims at reducing the risk of in-stent re-stenosis through the concomitant use of ionizing radiation applied through a cardiac catheter at the time of catheterization. This procedure involves exposing the revascularized vessel to beta or gamma radiation for a short period of time. The radiation can be delivered by a balloon system filled with a liquid radioactive isotope (e.g. rhenium-188), by isotopes (e.g. Iridium- 192) concealed in a ribbon or wire or by a radioactive stent. The term “brachytherapy” refers to radiation from a concealed source.

The procedure of intracoronary radiation, including the radiation plan and the handling, and the use and disposal of the radioactive sources, is strictly regulated because of the potential risks related to the exposure of patients and operating personnel to the radiation source.

REGULATION OF INTRACORONARY RADIOTHERAPY IN CANADA AND THE US

Canada

Both the Canadian Nuclear Safety Commission (CNSC) and Health Canada regulate intracoronary radiotherapy.

- CNSC licenses the use of the isotopes in the heart catheterization laboratory. The license specifies the isotopes that the catheterization laboratory is authorized to use.
- Health Canada has also approved two catheter-based delivery systems as class 4 medical devices:
 - Beta Cath (Novoste Corporation).
 - Galileo Intravascular Radiotherapy System (Guidant)Both systems delivers beta radiation.

United States of America

In November 2000, the Food and US Drug Administration FDA approved the same two radiotherapy delivery systems for the treatment of in-stent stenosis in native coronaries. The approval was based on brachytherapy’s demonstrated ability to significantly reduce in-stent restenosis. However, the FDA has not approved catheter balloon-filled radiation systems or radioactive stents. Nor has the regulator approved the clinical use of brachytherapy in de novo lesions.

In approving the devices, FDA required the following conditions to be met when the devices are being marketed [2]:

1. The label of the devices must include a warning to avoid the placement of new stents.
2. The label of the devices must advise users to maintain anti-platelet therapy for a minimum of 6 months after brachytherapy and for 1 year if a new stent is implanted.
3. Patients who were enrolled in the two FDA clinical studies before market approval must be followed for five years.

LITERATURE REVIEW

Objective

To assess the safety, effectiveness, and cost-effectiveness of using localized intracoronary radiation therapy in inhibiting in-stent restenosis following revascularization procedures. These will be compared to revascularization of in-stent restenosis without the concomitant use of radiation therapy.

Questions to be answered:

- Does intracoronary radiation inhibit in-stent restenosis following revascularization in the short term (6 months)?
- Does intracoronary radiation inhibit in-stent restenosis following revascularization in the long-term (3 years and longer)?
- What is the impact of intracoronary radiation on the occurrence of major adverse cardiac events including death, myocardial infarction and revascularization?
- Do intracoronary radiation procedures have any negative health impacts on the patient or health care staff involved? If so, what are these impacts and what are their rates of occurrence?
- Is intracoronary irradiation cost-effective?

Method

Inclusion Criteria

English language journal articles reporting primary data on the effectiveness or cost-effectiveness of intracoronary radiation therapy obtained in a clinical setting, or an analysis of primary data maintained in registers or institutional databases meeting the following criteria:

- Study design and methods are clearly described.
- Randomized controlled studies, non-randomized controlled studies or case series studies.
- The study is not superseded by a publication with the same purpose, by the same group, or a later publication that includes the data from centres involved in the same multicentre study (unless the articles address different endpoints).
- Reports of studies published between 1991– 2001.
- Review articles that provide insight on the subject matter.

Inclusion Criteria for studies

Subjects in the studies: Patients who have undergone revascularization of coronary arteries through balloon dilatation and stenting.

Intervention

Exposure to intracoronary gamma or beta radiation following revascularization. The control subjects would undergo similar revascularization procedure without intracoronary radiation therapy (received placebo in the form of sham radiation source).

Study period

Patients from the study group and the control group were followed for a period of six months or longer.

Outcome Measures (Study endpoints)

- Restenosis rates
- Presence or absence of restenosis and neointimal hyperplasia (determined by various methods including intravascular angiograph, intravascular ultrasound and/or echocardiogram).
- Changes in lumen diameter and/or volume; changes in morphology of vessel.
- Primary endpoints of death, myocardial infarction, and need for revascularization procedures.
- Any indication of complications/ill effects from the radiation on the patients or health care staff involved.
- Cost-effectiveness, cost utility or cost benefit information relating to the use of the procedure.

Exclusion criteria

- Interim reports on trials that have final results reported in a more recent article.
- Studies with less than 25 subjects.
- Studies focused on animal models and in vitro studies.
- Available only in a foreign language.
- Clinical trials published before 1991.

Databases & Search Strategy

Cochrane Library: Completed Reviews, DARE, Controlled Trial Register, CCOHTA, NICE, Economic Analysis Database, MEDLINE, other national and international HTA databases.
The search focused on human studies from 1991 - 2001

Cochrane: Use term “intracoronary brachytherapy”, “intracoronary radiation”

MEDLINE:

Search terms: Intracoronary brachytherapy, intracoronary radiation or intravascular radiaiton.

Limit: to human study

Search period: January 1991- December 2001

Search Results

Cochrane Database:

No articles were found in the Database of Systematic Reviews or DARE.

14 articles were found in the Cochrane Clinical Trial Register. These were among the articles on clinical trials obtained from MEDLINE.

MEDLINE

A final search on December 13, 2001 yielded 121 articles. The abstracts of the articles were screened according to the inclusion and exclusion criteria. One study has not been published but a presentation was found on a website. A total of 25 articles were reviewed and rated according to the following schema which is based on the hierarchy of clinical studies developed by Goodman :[40]

Table 1: Levels of Evidence

Type of Study (Design)	Level of Evidence	Number of Eligible Studies Analyzed
Large randomized controlled trial, Systematic reviews of RCTs	1	3 (2 RCT, 1 meta-analysis)
Large randomized controlled trial unpublished but reported to an international scientific meeting	1(g)	1
Small randomized controlled trial	2	10
Small randomized controlled trial unpublished but reported to an international scientific meeting	2(g)	
Nonrandomized trial with contemporaneous controls	3 a	
Nonrandomized trials with historical controls	3 b	
Surveillance (database or register)	4a	
Case series, multi-site	4b	
Case series, single-site	4c	11
Case series, multi-site, unpublished but reported to an international scientific meeting	4(g)	
TOTAL		25

Data Extraction and Synthesis

End points of the studies were summarized in Appendix I. A brief summary of the studies was provided in Appendices 2 and 3. Studies that focused on a specific aspect of intracoronary radiation therapy were not included in the Appendices, but were summarized in the text of this report. A complete list of references is included in the bibliography.

This report presents a descriptive synthesis of the available evidence. A meta-analysis was not conducted.

SUMMARY OF FINDINGS

Major Clinical Studies

Major randomized controlled trials on intracoronary radiation therapy using gamma radiation included Gamma-1, Coronary Radiation to Inhibit Proliferation on Post-stenting [SCRIPPS] trial, Washington Radiation for In-Stent Stenosis Trial [WRIST], Long-WRIST, WRIST Plus and WRIST-Crossover. The sample size ranged from 55 to 252. The follow-up period ranged from six months to three years.

The Proliferation Reduction with Vascular Energy Trial [PREVENT] is the only randomized controlled study using beta radiation sources for intracoronary radiation therapy. This study included 105 subjects. Beta – WRIST, part of the WRIST trial, compared the six-month outcomes of 50 patients from a prospective beta radiation registry to those of controls from the Gamma Wrist Trial. The other clinical studies on beta radiation were case series such as the Beta Energy Restenosis Trial [BERT], the Milan Dose-Response Study, the European dose finding study, and studies by Kozuma and Meerkin on morphological change and plaque growth. The sample size of these studies ranged from 30 to 181. In addition, two small trials (with 21 and 28 patients respectively) studied the use of a liquid beta radiation

source (188-Re filled balloon). Stents and Radiation Therapy Trial [START], a multicenter randomized controlled trial with 476 patients with in-stent restenosis, has not been published but was presented at the 2000 conference of the American College of Cardiology.

No randomized controlled trials were found on the use of radioactive stents. Three small case series were found.

Other studies focused on complications or morphological impacts of intracoronary radiation therapy.

The outcomes of the studies are summarized in **Appendix I to III**. Details of the studies are summarized in **Appendices IV**. The major findings are discussed below.

Sources of ionizing radiation used in Studies

Isotope	Type of Radiation	Radiation Source	Method of Delivery
Iridium - 192	gamma	Seed trains concealed in ribbon (Checkmate system, Cordis) or Radioactive wire	Manual after loader
Yttrium-90	beta	Radioactive wire	Manual afterloader
Strontium-90	beta	Radioactive wires (Beta-Cath, Novoste)	
Strontium/Yttrium-90	beta	SeedsRadioactive wire	Manual
Phosphorus-32	beta	Radioactive stent (Isostent)	Manual
Phosphorus-32	beta	Radioactive wire (Guidant)	Manual
Rhenium – 188 or Re-186	beta	Liquid Re-188	Manual, balloon catheter

Adapted from Table 1, Waksman, 1999

Major Adverse Cardiac Events

Major adverse events [MACE] include death, myocardial infarction and target lesion revascularization or target vessel revascularization. Significantly lower rates of MACE were reported for irradiated groups than controls in studies including GAMMA 1 (28.2% vs 43.8% at 9 months), Scripps Trial (23.1% vs 55.2%), Gamma WRIST (35.3% vs 67.6%), and Beta WRIST (46% vs 72% at 2 years).[5, 9, 8, 7] These reductions in MACE rates were not determined by reduced incidence of death or myocardial infarction, but were determined solely by a diminished need for revascularization of the target lesion. The PREVENT Trial did not find a significant difference in the incidence of MACE between the irradiated group and the controls.

Mortality Rate

Reported mortality rates for irradiated patients ranged from 0% at six months in the Beta-WRIST Trial [8], to 10% in the two year WRIST follow-up [7], and 11% at three years in the SCRIPPS Trial.[9] These rates were not found to be significantly different from the placebo controls.

Restenosis Rate

Significant reductions in 6-month angiographic restenosis rates were reported for patients who received either gamma or beta radiation compared to the controls. These reductions in target lesion restenosis rate

ranged from 41% in Gamma-1 and 56% in Beta-WRIST, to 63% in Gamma WRIST and 66% in PREVENT. The reductions in restenosis rate were believed to be a combined effect of an increase in proximal and distal external elastic membrane area[12], inhibition of neointimal formation[13], and positive remodeling[14] as a result of radiation therapy.

The two-year WRIST follow-up trial showed that the clinical benefit of intracoronary radiotherapy occurred predominantly in the first 6 months after the index procedure. The SCRIPPS study reported that although angiographic restenosis was reduced by 69% at 6 months, the reduction was only 48% at 3 years because of small reductions in luminal diameter over the long follow-up period [9]. However, the reduction in restenosis rate at 3 years was still significant.

Significant late lumen loss had been reported by other studies.[15, 16, 17, 18, 19] These findings were consistent with the increase in neointimal proliferation observed after the 6 months period. Shiran[20] conducted intravascular ultrasound studies on irradiated and non-irradiated lesions and found that lumen loss resulting from increased tissue in the stent correlated with lesion length and preintervention in-stent tissue, but was not reflected in qualitative coronary angiography.[20]

Edge Stenosis

Despite the significant reduction in restenosis rate, stenosis at the proximal and distal edges of the irradiated segment (edge effects or candy-wrapper effect) has been reported for both gamma and beta-irradiated patients.[7] Six-month angiography in the Gamma WRIST TRIAL showed that restenosis occurred predominantly at the edges of the irradiated segments but was more diffuse in the placebo patients. The Milan Dose Finding Trial reported edge stenosis in 40-52% of the patients who received beta radiation from radioactive stents.[17] Latchem et al[21] also reported edge stenosis in 13% of the patients treated with beta radiation.

Sianos[22] studied the vessels of 175 subjects treated with beta radiation in the BRIE study, using quantitative coronary angiography. This study showed that geographical miss in radiation affected 41.2% of the edges. Geographical miss is a situation in which the radiation source does not fully cover the injured segment. The study further showed that the mean restenosis rate of the geographical missed edges was significantly higher than that of the non-geographical missed edges (16.3% versus 4.3%). Sianos[22] concluded that geographical miss is strongly associated with restenosis at the edges of the effective irradiated segment. Parikh et al[23] and Kim et al[24] reported similar findings. Other studies suggested that edge effects might be associated with vessel injury from the balloon during dilatation.[19]

Target Lesion Revascularization Rate [TLR]

All studies reported that intracoronary radiation significantly reduced the need for target lesion revascularization. Target lesion revascularization rates in the irradiated groups ranged from 6% (PREVENT 1 year)[6] to 42 % in the Beta WRIST (2 year follow up).[7] These represented 36% (Beta WRIST) - 75% (PREVENT) reductions in TLR rates, with a median reduction of approximately 58%.

Target Vessel Revascularization Rate [TVR]

Reductions of 33 % (Gamma-1) – 53% (Beta WRIST) in target vessel revascularization rates were observed in the irradiated groups of the various studies. Although these reductions were not as high as the reductions in TLR rates, they are still significant. The Gamma WRIST Trial showed a 9.3% increase in TLR and a 7.6% increase in TVR in the irradiated group between 6 and 12 months. This was not observed in the placebo group.[7]

Late Thrombosis and Occlusion

Late thrombosis is defined as thrombosis occurring after 31 days following the index procedure. This phenomenon is rarely seen following conventional coronary intervention such as balloon dilatation or regular stenting.[25]

Late thrombosis has been observed in patients following both gamma and beta intracoronary radiation therapy. Raizner et al[16] reported that 7 out of 80 patients (9%) in the irradiated group of the PREVENT Trial suffered myocardial infarction due to late thrombosis. Latchem et al[21] reported late thrombotic occlusion in 7% of patients who received intracoronary beta radiation. The Gamma -1 Trial[5] reported that at 9 month follow-up, late thrombosis occurred in 5.3% of the irradiated group compared with 0.8% of the placebo group, resulting in more late MI in irradiated patients (9.9% versus 4.1%). Waksman et al[25] suggested that late thrombosis associated with coronary radiation therapy may be caused by delayed healing of small dissections at the stent edges, regression of tissue at the outer side of the stent, or incomplete/impaired reendothelialization.

The Gamma -1 Trial[26] found that late thrombosis occurred in irradiated patients only after the discontinuation of oral anti-platelet therapy and only in patients who had received new stents at the time of the radiation treatment. A six month study (WRIST Plus) of 120 patients who received ongoing clopidogrel and aspirin following intracoronary gamma radiation, showed a reduction in late thrombosis rate compared to a similar cohort treated with only 1 month of clopidogrel and aspirin.[26]

A two year follow-up of the WRIST TRIAL[7] showed that intracoronary radiation was associated with high rates of late occlusion (12% in beta-WRIST and 8% in gamma-WRIST) of the culprit lesion, with most presenting with a clinical event within the first six months following the index procedure. However, the late total occlusion rates at 2 years were not significantly different between the irradiated and the control subjects. Late coronary occlusion was also reported by other studies including a series of 108 patients who received beta radiation in which 6.6% of the patients suffered sudden thrombotic events 2-15 months after radiation.[27] [21] [27]

To explain findings of late lumen loss, late thrombosis and occlusion, and late increase in revascularization, Waksman et al[7] suggested that radiation therapy might delay the restenotic biologic process that is reestablished beyond 6 months. The authors also cautioned that potential risk of late effects of radiation may occur up to 10 years after the procedure.

The unpublished Stents and Radiation Therapy Trial [START][39] showed similar trends in reduced in-stent restenosis, revascularization rates and MACE at 8 months. However, it did not find any late thrombosis among irradiated patients with new stent placement.

Factors That May Influence Efficacy

Dose Effect

The European Dose Finding Trial[28], a multicentre, randomized study, evaluated the effect of 9, 12, 15 and 18 Gy of beta radiation (Y-90 source) on de novo lesions in native coronary arteries of 181 patients. The results showed that intra-coronary beta radiation therapy produces a significant dose-dependent decrease in the rate of restenosis after balloon dilatation. The study reported that an 18-Gy dose not only prevents the renarrowing of the lumen typically observed after successful balloon dilatation, but actually induces luminal enlargement.[28]

The Milan Dose-Response trial[17] studied the dose effect of P-32 emitting stents on 91 de novo lesions in 82 patients. Three doses were used. The six month results showed that intrastent neointimal hyperplasia was reduced in a dose-related manner with a binary stenosis rate of 16% for the lowest dose group and 0% in the group with the highest dose [17]. These results may have limited generalization because de novo lesions instead of in-stent re-stenoses were studied.

A smaller series conducted by Meerkin et al[13], with 30 patients using beta radiation from Sr-90, showed no significant dose effect [13].

Length of the Lesion

Long lesions present an additional challenge for treatment because the occurrence of clinical restenosis appears to increase with the length of the stent. Studies have shown reduced efficacy of intracoronary radiation therapy in diffuse in-stent restenosis. One possible explanation is that longer lesions have more aggressive neointimal proliferation. Another is that the source-to-target distance is greater in long lesions.[12]

As part of the WRIST Trials[12], serial intravascular ultrasound was used to assess the efficacy of gamma radiation therapy on long lesions (36 – 80 mm) in 30 irradiated patients and 30 controls from the Long-WRIST trial. In addition, 25 patients from the Long WRIST High Dose Registry were also evaluated for comparison. Minimum cross sectional area of the lumen was used as a measure. The results showed that gamma irradiation was effective in reducing recurrent in-stent neointimal hyperplasia in long, diffuse in-stent restenotic lesions. However, it was even more effective when given at a high dose.[12]

The effect of post-radiation anti-platelet therapy and placement of new stents have been described under late thrombosis.

Safety and Efficacy of Types of Intracoronary Radiation

Studies have shown that a significant reduction in in-stent restenosis can be achieved using Ir-192, P-32, or Y-90 in the form of seed trains or wire. A small case series using liquid Re-188 showed that the system is feasible and safe [16]. The WRIST Trials showed that beta and gamma radiation were equivalent in all clinical endpoints assessed at two years [7].

Three case series using P-32 radioactive stents yielded less favorable results. Based on a series of 82 patients, Albiero et al[17]reported that the use of P-32 beta-emitting stents was feasible but resulted in high intra-lesion restenosis rates (40 – 52 %) at all three dose levels, because of high late luminal loss at the stent edges (edge effect)]. Wardeh also reported high in-stent restenosis in a series of 31 patients, but with no edge effects.[19]. In a series of 40 patients, Kay et al[18] concluded that neointimal proliferation is delayed rather than prevented by radioactive stent implantation, and that clinical outcome at one year is not favorable when compared with conventional stenting.

Logistic Issues of Providing Intracoronary Radiation Therapy

Radiation oncologists from 12 sites (in the United States) that have participated in double blinded, randomized controlled trials of intracoronary radiation therapy, completed a questionnaire designed to identify logistic issues faced by these practitioners.[29] The study identified several logistic issues relating to intracoronary radiation therapy:

- Regulatory issue: The survey showed that licensing was perceived as a substantial hurdle; approval by the Nuclear Regulatory Commission [NRC] in the USA took more than 5 months at five of twelve sites. In addition, approval from the institutional review board and informed consent from the patient were also required for the studies.
- Radiation oncologist-patient interaction: It was reported that 75% of the radiation oncologists did not see patients prior to the procedure and were not involved in obtaining informed consent.
- Scheduling issue and time commitment: The mean time spent per case was reported to be 30-90 minutes with a mean of 60 minutes. This included time for the required documentation. The radiation oncologists expressed major concerns about after-hour coverage and case scheduling. Less than 50% of the radiation oncologists had input in case scheduling.
- Lack of role delineation: Neither the study protocols nor the Food and Drug Administration specified the actual roles of the radiation oncologists and the interventional cardiologists. Thus, the exact roles of these individuals were left to the discretion of each center. NRC mandates that the radioactive source ribbon must only be handled by a radiation oncologist. The medical physicist was involved in calculating the dwell time that is checked by the radiation oncologist.
- The need for working relationship between the radiation oncologists and interventional cardiologists.

The survey concluded that the above issues need to be addressed before intracoronary radiation therapy becomes a part of widespread clinical practice.[29]

Clinical Studies/Registries in Progress

Some large randomized controlled trials and registries to evaluate the effectiveness of intracoronary radiation therapy are in progress and the results are pending. These include:

- Intimal Hyperplasia with Beta In-stent Trial [INHIBIT], a randomized, double blind, multicentre study using P-32.
- BETACATH – a large multicenter, placebo-controlled trial using beta irradiation from Sr-90/Y source.
- Angiorad Radiation Therapy for In-Stent Restenosis IntraCoronary Trial [ARTISTIC] is a two centre randomized trial studying the effect of gamma radiation for difficult lesion subset.
- Angiorad Radiation for REStenosis Trial [ARREST] – evaluates the Angiorad system.
- European Surveillance [RENO] Registry aims to determine effectiveness at 6 months.

Alternative Technologies

Other adjunctive technologies for treating in-stent restenosis include the use of more potent oral anti-platelet drugs (e.g. combination of aspirin and ticlopidine) following percutaneous interventions and plaque reduction using laser angioplasty or atherectomy devices. Laser angioplasty and atherectomy devices have not been shown to be effective in reducing restenosis.

Patients would have to undergo CABG should all the above procedures prove to be inadequate in preventing restenosis.

A developing technology that holds promise for preventing in-stent restenosis is the drug eluting stent. These stents contain drugs that diffuse from the stent to either inhibit thrombosis or inhibit intimal hyperplasia at the stent site in an attempt to reduce the risk of restenosis. Drug eluting stents are currently under clinical evaluation. Preliminary results appear to be encouraging.[30]

A recent publication reported that treatment with a combination of folic acid, vitamin B12 and pyridoxine significantly reduces homocysteine levels, and decreases the rate of restenosis and the need for revascularization of the target lesion after coronary balloon dilatation.[31]

SYNOPSIS AND CRITIQUE OF EVIDENCE

The main findings of the literature review are summarized below

- There were 3 randomized controlled trials on catheter-based gamma radiation : the Scripps Trial, the Washington Radiation for In-stent Restenosis Trial [WRIST] GAMMA-1) and two randomized controlled trials on catheter-based beta radiation (PREVENT and START) (Levels 1–2).
- There were no randomized controlled trials on liquid-filled balloon systems or radioactive stents.
- Based on Levels 1 and 2 evidence, catheter-based gamma and beta intracoronary radiation appear to be safe in the short term.
- Catheter-based gamma radiation and beta intracoronary radiation appear to be effective in the short term as an adjunct therapy in significantly reducing angiographic and clinical in-stent restenosis following successful revascularization procedures.
- Catheter-based intra-coronary radiation lowers the incidence of major adverse cardiac events as a result of reduction of the need for target-lesion and target-vessel revascularization. This effect has been shown to sustain for up to three years. However, there is a rapid increase in revascularization need between six months and two years following irradiation.
- The major complications associated with intracoronary radiation are:
 - Late thrombosis, late luminal loss and in some cases, late total occlusion. Late thrombosis increases the risk of myocardial infarction. The placement of new stents at the time of radiation may contribute to this complication.
 - Restenosis at the proximal and distal edges (“candy-wrapper effect) of the irradiated segment of the vessel. Geographic miss has been proposed as a possible cause for edge stenosis.
- Prolonged antiplatelet therapy and a reduction in the number of new stents placed at the time of radiation have been shown to reduce the rate of late thrombosis.
- The evidence on intracoronary radiation using liquid-filled balloon systems is limited. Randomized studies comparing this type of radiation to placebo have not been reported.
- Intracoronary radiation therapy using radioactive stents does not appear to be as effective as catheter-based intracoronary radiation systems. High rates of stenosis at the edges of the radiated segment have been reported.
- Long-term safety and effectiveness of intracoronary radiation have yet to be established.
- No comparison can be made regarding the effect of intracoronary radiation on in-stent lesions versus de novo lesions. The role of brachytherapy in de novo lesions has not been clearly established.

Expert Opinion:

- In a January 2001 review, Drs. R. Sheppard and M. Eisenberg[34] at the Jewish General Hospital in Montreal indicated that intracoronary brachytherapy is a new and exciting technology that is in its infancy. They believe that some questions remain to be answered including:
 - Safety issues around the handling of radioactive isotopes in the catheterization lab.
 - Long - term complications such as carcinogenic risk, coronary aneurysms and complete thrombosis.
 - Long - term efficacy.

The authors (and other investigators) identified the need for long-term clinical trials with larger numbers of patients. They advised that physicians should be cautious in using the procedure until there is sufficient evidence to assess whether the benefits of the procedure outweigh its risks.

- A January 2001 review by the FDA[2] showed that it has concerns similar to those expressed by Drs. Sheppard and Eisenberg.

ECONOMIC ANALYSIS

No literature on economic analysis was found.

CITITQUE OF EVIDENCE

The quality of the evidence is limited by the following factors:

- With the exception of the WRIST, PREVENT, SCRIPPS and GAMMA 1 Trials, the majority of the studies are case series with no randomization, control or blinding.
- Of the clinical trials reviewed, only GAMMA 1 is a level 1 with 252 subjects. All the other studies have small sample sizes (under 200). Level 2 & 3 studies were found for both gamma and beta radiation.
- With the exception of the Scripps trial and the WRIST Trial, none of the other studies exceeded 12 months of follow-up. The longest trial period is three years.
- There is heterogeneity relating to the type of lesions studied. Some studies such as SCRIPPS, WRIST and GAMMA 1 included only subjects with in-stent restenosis. Other studies such as PREVENT and the study by Hoher (2000) included both in-stent restenotic lesions as well as de novo lesions while a third group of studies (Milan Dose Trial, BERT, Verin and Meerkin) included only de novo lesions. This heterogeneity posed a challenge for the comparison of outcomes and external validity. Moreover, some studies only included native vessels while others also include grafts.
- There is also intra-study and inter-study heterogeneity in revascularization procedures used. In most studies, one or more technologies were used for revascularization including balloon dilatation, laser angioplasty, atherectomy and additional stenting. Decisions were made on an individual basis at the discretion of the surgeons.
- There is heterogeneity in the duration of anti-platelet therapy following revascularization and intracoronary radiation therapy. This may account for some of the variation in revascularization rates following irradiation.

GUIDELINES FOR USING INTRACORONARY RADIOTHERAPY

The procedure and protocol for planning and delivering intracoronary radiotherapy is very complex. Health Canada provided indications for using the two approved systems. The complexity is demonstrated in the perspectives of the American Brachytherapy Association (Appendix V)[36], and in the Draft American College of Medical Physics (ACMP) Standard for Intravascular Brachytherapy (<http://www.acmp.org/standards>)

Indications for Use (Health Canada)

The GALILEO Intravascular Radiotherapy system:

For single-vessel radiotherapy in patients with symptomatic ischemic heart disease due to discrete de novo or re-stenotic native coronary arteries lesions with a reference lumen diameter from 2.4 mm to 3.7 mm.

Contraindications: Pregnancy, unprotected left main, coronary artery spasm, severe tortuosity, previous radiotherapy to the heart or target site, bifurcation lesions, SVG or IMA grafts.

The Beta Cath Delivery Catheter and Accessory Pack

Is to reduce the incidence of restenosis and is indicated for use as an adjunctive procedure in patients with ischemic heart disease, who present with a single lesion which is treated with a 20 mm balloon, with a reference vessel diameter of 2.5 - 3.5 mm.

Contraindications: Unprotected left main disease (50% narrowing), patient undergoing or having prior chest radiotherapy and presence of a curve at lesion site less than 45 degrees.

SUMMARY OF STUDY OBSERVATIONS

The short-term effectiveness of catheter-based intracoronary radiation using radiative seed trains in reducing in-stent restenosis and the need for revascularization procedures has been confirmed through a number of prospective randomized clinical trials, at least one of which is Level 1 quality evidence. The evidence on liquid-filled balloon system is limited and radioactive stents were shown to have limited effectiveness. The long-term effectiveness of intracoronary radiation, particularly procedures using beta sources, has yet to be established.

Of particular concern are two complications that have been consistently reported in the studies. These complications are late thrombosis leading to myocardial infarction and stenosis in the edges of the radiated segment. This concern is compounded by the lack of cost-effectiveness information and Ontario guidelines for the use of this technology.

The issue of coronary vessel re-stenosis is an extremely important treatment issue to address. The role of alternative technologies such as drug eluting stents needs to be explored.

APPENDIX I- SUMMARY OF CATHETER-BASED GAMMA INTRACORONARY RADIATION STUDIES

Intervention and End Point	SCRIPPS Teirstein Ps, 2000	WRIST (Gamma) Waksman R, 2000	WRIST Wakman R, 2001	GAMMA ONE Leon MB, 2001	WRIST PLUS Waksman , 2001	WRIST Crossover Wakesman 1999	Wakesman 2000
Type of Study/level of evidence	RTC Level 2	RTC Level 2	RTC Level 2	RTC Level 1 Multicenter	Historical control, Level 3b	RTC Level 2	Retrospective analysis of RTC
Follow-up	3 years	12 months	2 years	9 months		6 months	At least 6 months
Number of subjects	N study = 26 N control = 29 (in-stent restenosis)	N study = 65 N control = 65 (in-stent restenosis)	N gamma=50 N Beta = 50 N Control = 50	N study = 131 N control = 121 (in-stent restenosis)	N study = 120 N control = Radiat. 125 Placebo 126	N primary = 65 N crossover = 39 (in-stent)	N study = 308 N control = 165
Intervention: Study subject: Control: All:	192 - Ir gamma Sham radiation New stents – aspirin, ticlopidine 2 wks	192 -Ir gamma ra Sham radiation Ticlopidine: 1 mo	192-Ir gamma 90-Y Beta Control: sham rad	192- Ir gamma rad Sham radiation -Aspirin & clopidigrel 8 wks	Gamma radiation Clopidogrel & Aspirin for 6 mos, vs 1 month for controls (in- stent)	192-Ir Gamma Control- sham radiation- crossover	Gamma or beta radiation & anti-platelet therapy New stent: Irradiated 82% Control 100%
Restenosis rate Radiation Placebo	In-lesion 33.3% 63.6%	Instent In-lesion 19% 22% 58% 60%		Instent In-lesion 21.6% 32.4% 50.5% 55.3%	% of patients 26 (rad. Wrist Plus) 27 (rad. Wrist)		
TLR Rate Radiation Placebo	15.4% 48.3%	23% 63.1%	Beta 42% Gamma 32% Placebo 66%	24.4% 42.1%	21 (WRIST PLUS) 22 (WRIST) 60 (WRIST control)		
TVR Rate Radiation Placebo	31% 59%	34% 68%	Beta 46% Gamma 44% Placebo 72%	31% 46%	23 (WRIST PLUS) 30 (WRIST) 63 (WRIST control)		
MACE: Radiation Control	23.1% 55.2%	35.3% 67.6%	B=46% γ = 48% 72%	28.2% 43.8%		Primary =29% Cross over = 25.6%	
Myocardial Infarction Radiation Placebo	3.9% 10.3%	9.2% 9.2%	Beta 0 Gamma 0 Control 0	9.9% 4.1%			Acute MI 43% Radiation pts
Death Radiation Placebo	11.5% 10.3%	6.2% 6.2%	Beta 8% Gamma 10% Placebo 10%	3.1% 0.8%	1.7 (WRIST PLUS) 4.8 (WRIST) 4.8 (WRIST control)	Primary 4% Crossover 8%	
Late Thrombosis Radiation Placebo	4% 0%	9.2% 3.5%	Late total occlusion not signif. different	5.3% 0.8%	2.5 (WRIST PLUS) 10 (WRIST) 1 (WRIST control)	Primary 9.6% Crossover 15.4%	
Other findings	Mean min luminal diameter decreased between 6 mos. & 3 yrs in rad. group	Radiat. Gp increase in revascularization between 6 & 12 months	Between 6 mos& 2 yrs, 14% TVR in both rad. Gps.	Late in-stent luminal loss: Rad. 0.73+/- 0.79mm Control 1.14+/- 0.65mm			Late total occl. ∴ Irradiated 9.1% Control 1.2%

TLR = Target Lesion Revascularization

TVR = Target Vessel Revascularization

MACE = Major adverse cardiac events

APPENDIX II– SUMMARY OF CATHETER-BASED BETA INTRACORONARY RADIATION STUDIES

Intervention and End Point	WRIST (Beta) Waksman R ,2000	PREVENT Raizner AE, 2000	START Popma J, 2000 (Presentation)	Costa et al 1999	Kozuma et al 2000	Latchem et al 2000
Type of Study/level of evidence	Prospective registry Level 4a	RTC Level 2	RTC Level 1 g Multicenter	Case series Level 4c	RTC Level 2	Case series Level 4c
Follow-up	6 months	12 months	8 months	6 months		7+/-4.5 months
Number of subjects	N study = 50 N control = 50 (hx) (in-stent restenosis)	N study = 80 N control = 25 (de novo/ in-stent)	N study =244 N control = 232	N = 108	N rad. = 18 N contr. = 13	N = 37 (in-stent)
Intervention: Study subject: Control: All:	90-Y beta rad wire Sham radiation (anti-platelet drug for 1 month)	P32 beta rad.@ 3 dose levels Sham radiation New stent-ticlopidine 4 wks	90-Sr beta rad. Sham radiation Aspirin & ticlopidine 60 or 90 days	Beta radiation following balloon dilatation	Catheter based beta radiation Sr 90/Y 90	Strontium 90 Beta radiation
Restenosis rate Radiation Placebo	Instent In-lesion 22% 24.1% 66.7% 71.1%	Instent In-lesion 8% 22% 39% 50%	Instent In-lesion 14.2% 18.2% 41.2% 45.3%			10%
TLR Rate Radiation Placebo	28% 66%	6% 24%	13.1% 22.4%			
TVR Rate Radiation Placebo	34% 72%	21% 32%	16.0% 24.1%			19% (6 months)
MACE: Radiation Control	34% 76%	16% 24%	18% 25.9%			
Myocardial Infarction Radiation Placebo	10% 14%	10% 4%	-			0%
Death Radiation Placebo	0% 8%	1% 0%	-	6.6%		8%
Late Thrombosis Radiation Placebo	10% 4%	4% 0%	0 0			7% Edge effect 13%
Other findings		edge stenosis reported Late lumen loss Rad. 0.2+/-0.6mm Control 1.1+/-0.7mm		Factors: overlapping stent, unhealed dissection or radiation?	Effective dose may alter the biophysiological process on plaque growth	Success rate=97%

APPENDIX III: SUMMARY OF STUDIES ON CATHETER-BASED INTRACORONARY RADIATION AND RADIOACTIVE STENTS

Study Designs and Outcomes	Meerkin D et al 1999	Verin et al 2001 (untreated)	King SB 1998 (BERT)	Hoher M et al 2000	Albiero R et al 2000	Kay IP et al 2001	Wardeh AJ 1999
Type of study/Level of evidence	Randomized No control Level 4c	Prospective study, no control Level 4c	Case series Level 4c	Case series Level 4c	No control 4c Level 4c	Case series Level 4c	Case series Level 4c
Follow up period	> 6 months	6 months	6 months	6 months	6 months	1 year	6 months
Number of subjects	N = 30 (de novo lesions)	N = 181 (De novo)	N = 37 (de novo)	N = 28 De novo & restenotic	N = 82 (de novo)	N = 40 (de novo)	N = 26 97% successful placement
Intervention	3 gps received different doses of beta radiation Sr 90	Balloon dilatation, then 9, 12,15 or 18 Gy of Yttrium -90 beta rad.	Beta radiation Novoste Beta Cath after balloon dilatation Success 91%	Beta radiation Liquid 188-Re filled angioplasty balloon	32-P beta radioactive Stents (0.75-3 uCi, 3-6 uCi or 6-12 uCi)	32-P beta radioactive stent 6-12 Ci	32-P beta radioactive stent 0.75 – 1.5 Ci over 100 days
Restenosis Rate	10%	Decreased Dose dependent			Intrastent decreased with dose	Significant in-stent luminal deterioration 6 months – 1 year	17/23 (74%) in-stent
TLR	10%		9.5%	12%			56% revascularization
TVR	17%			46%			
MI			0			23%	No adverse in hosp cardiac event
Death			0		0		
Late Thrombosis					4 total occlusion including 1 stent thrombosis	No late occlusion, MI or death. 65% remained event free @ 1 year	Loss of lumen diameter of 0.99+/-0.89 mm
Edge stenosis				32%	40–52% Stenosis decreased with radiation dose.		None
Finding	No significant dose effect	86% no serious complications -18 Gy induces luminal enlargement	Late lumen loss= 0.05mm Late loss index = 4%	Late lumen loss			

APPENDIX IV – DETAILED SUMMARY OF STUDIES

Study (Reference)	Method	Results	Conclusion	Level of Evidence
<p>Teirstein PS et al Three-year clinical and angiographic follow-up after intracoronary radiation: results of a randomized clinical trial Circulation 2000 Feb 1;101(4):350-1 (SCRIPPS Trial) USA</p>	<p>A total of 55 patients enrolled. All had previous restenosis after coronary balloon dilatation. 26 randomized to receive 192-Ir radiation & 29 to placebo. Followed for 3 years for restenosis rate through angiographic follow up.</p>	<p><u>At 3 yrs:</u> Target lesion revascularization significantly lowered in the Ir gp (15.4% vs 48.3%). Restenosis rate was also significantly lower in the radiated gp (33% vs 64%). Mean minimal luminal diameter between 6month – 3yrs decreased in radiated gp but remained unchanged in placebo patients.</p>	<p>Early clinical benefits observed after treatment of coronary restenosis with 192-Ir appear durable at late follow-up but a small amount of late loss was observed between 6 months and 3-year follow-up. At 3-year follow-up, vascular radiotherapy continues to be a promising new treatment for restenosis.</p>	<p>Level 2 Double blind randomized placebo controlled study Long follow-up: 3 years.</p>
<p>Waksman R et al Intra-coronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. Circulation 2000 May 9;101(18):2165-71 WRIST USA</p>	<p>130 consecutive with previous intracoronary stent implantation in coronary arteries (100 native coronaries, 30 AC by-pass grafts) underwent successful balloon dilatation with the use of balloons, ablative devices or additional stents. <u>Pts were randomized to:</u> Study gp: 65 pts (63+/-10.9 yrs) received gamma radiation from a nylon ribbon containing seeds of ¹⁹²Ir Controls: 65 pts (62+/-10.2 yrs) received a nylon ribbon containing a placebo. Angiogram & intravascular ultrasound performed after the procedure. All pts received ticlopidine for 1 month. <u>Follow-up</u> Angiography at 6 months & clinical follow-up @ 1, 3, 5 & 12 months.</p>	<p><u>Pre-radiation Intervention:</u> Balloon dilatation alone-10.7% Atherectomy: 60% of native coronaries Excimer laser in 90% of vein grafts Restenting- 35.4% of the lesions. 2 pts from study gp & 2 pts from the placebo gp did not complete the treatment. <u>In hospital & after 30 days:</u> No deaths, subacute closure or Q-wave MI in either gp. <u>6 month angiograph showed:</u> In-stent restenosis in radiation gp 67% < placebo gp Stenosis in segment including stent edges 63%< placebo gp Target lesion revascularization: Radiation: placebo= 13.8%: 63.1% Target vessel revascularization: Radiation: placebo =26.2%: 67.7% Freedom from major cardiac event: radiation: placebo=29.2%: 67.7% Ultrasound showed evidence of intimal hyperplasia regression in radiation gp. <u>At 12 months:</u> 9.3% increase in target lesion revascularization and 7.6% increase in target vessel revascularization in radiation gp.</p>	<p>Intra-coronary gamma-radiation used as adjunct therapy for patients with in-stent restenosis significantly reduces both angiographic and clinical restenosis. Late luminal loss found to be less at the center of the lesion compared with the edges. Late thrombosis observed more in the radiation gp.</p>	<p>Level 2 Prospective, randomized, double-blind trial</p>

Study (Reference)	Method	Results	Conclusion	Level of Evidence
Waksman R et al Intracoronary [beta]-Radiation Therapy inhibits recurrence of in-stent stenosis. Circulation 2000 April;101(16):1895-1898. Beta WRIST	Prospective registry – 50 consecutive patients with ISR in native coronaries underwent balloon dilatation, laser angioplasty, rotational atherectomy and or stent implantation before receiving a dose of 20 Gy of beta radiation from a system using a 90-Yttrium beta emitting wire. Follow-up for 6 months	Manual stepping up of the radiation catheter necessary in 17 patients with lesions >25mm long. -At 6 months, binary angiographic restenosis rate was 22%, the target lesion revascularization rate was 26% and the target vessel revascularization rate was 34%. All rates were significantly lower than those of the placebo group of Gamma-WRIST.	Results suggest that intracoronary beta radiation using 90-Yttrium may be a viable therapeutic option for patients with ISR. These findings need to be corroborated in randomized controlled trials.	Surveillance based on registry. Level 4a
Waksman R et al Two year Follow-up after Beta and Gamma Intracoronary Radiation Therapy for patients with Diffuse In-stent-stenosis The American Journal of Cardiol 2001 August;88(4):425-428. WRIST follow-up	2 year follow –up of Gamma WRIST N = 50 Received 125-Ir radiation Placebo from Gamma WRIST N =50, received sham radiation Beta WRIST N = 50 Control from Gamma WRIST N =50 Clinical follow-up @ 6, 12 & 24 months. No two year angiography	All pts completed follow-up -No significant difference in rates of death or MI among the 3 groups MACE: Beta 46%, placebo 72% Gamma 48% TLR Rate: Beta 42%, placebo 66%, gamma 32% TVR: Beta 46%, placebo 72%, gamma 44% Signif. Rates of TVR in both radiation gps, not placebo gp	Evidence of long-term efficacy of beta and gamma radiation as adjunctive therapy to coronary intervention in treatment of ISR. -Benefit mainly in first 6 months after procedure -Higher rates of revascularization evident beyond 6 months to 2 yrs in both irradiation gp. -Late total occlusion seen at 6 months not seen @ 2 years.	Level 2 -3 Randomized controlled trial & non-randomized compared to historical control Small sample
Waksman R et al Intra-coronary radiation for patients with refractory in-stent restenosis: an analysis from the WRIST-Crossover Trial. Washington Radiation for In-stent Restenosis Trial. Cardiovasc Radiat Med 1999 Oct-Dec; 1(4): 317-22 USA	104 pts with in-stent restenosis were randomized to: Study gp: 65 pts received gamma irradiation 192-Ir Control gp: 39 pts treated with placebo then cross over to irradiation when presented with ISR & angina. Monitored at 6 months for mortality, morbidity and TLR	At 6 months, the rate for multiple adverse cardiac events was 25.6% in the crossover group vs. 29% in the primary irradiation gp. Three pts in the crossover gp & 4 in the primary treatment gp died. 9.6% with late thrombosis and 6.2% has total occlusion in the primary treatment gp vs 15.4% in the crossover gp.	Patients who failed conventional catheter-based intervention without radiation can be treated with 192-Ir with results similar to those who initially receive brachytherapy.	Level 2 Prospective Randomized controlled study Short duration
Amed Waksman R et al Serial intravascular ultrasound assessment of the efficacy of intracoronary [gamma]-radiation therapy for preventing recurrence in very long, diffuse, in-stent restenosis lesions. Circulation 2001 August;104(8):856-859 (Long WRIST, HD WRIST)	Used serial intravascular ultrasound to study pts with lesions 36-80mm long. Long WRIST RTC (30 irradiated, 34 placebo pts) Long WRIST High Dose Registry N= 25 irradiated pts.(18 GY at 2 mm from the source.) Stent, lumen & intimal hyperplasia measured at 2 mm intervals.	@ 6 months follow-up, more lesions in L anterior descending artery & excimer laser used more often in HD Long WRIST pts. -Baseline measurements similar. -Follow-up minimum cross sectional area (CSA) smaller in placebo patients; significantly smaller in Long WRIST than HD Long WRIST patients.	Results showed that gamma irradiation reduces recurrent in-stent neointimal hyperplasia in long, diffuse ISR lesions, however, it is even more effective when given at high dose. (10% of the total Long WRIST cohorts and 7% of the High Dose Long WRIST cohorts had total occlusions at follow-up)	Level 2-4

Study (Reference)	Method	Results	Conclusion	Level of Evidence
<p>Raizner AE et al Inhibition of restenosis with beta-emitting radiotherapy: Report of the Proliferation Reduction with Vascular Energy Trial (PREVENT). Circulation 2000 Aig29;102(9):951-8</p> <p>USA</p>	<p>Study at 6 clinical sites. 105 pts with (70% de novo & 30% restenotic lesions) were treated with by stenting (61%) or balloon dilatation only (39%). Randomized into 4 groups I. 25 pts received 0 Gy radiation (control) II. 26 pts received 16 Gy radiation from ³²P encapsulated in Nitinol wire. III. 27 pts received 20 Gy from a similar source IV. 27 pts receive 27 Gy from a similar source All pts received aspirin for the duration of the study. Pts who received a stent received Ticlopidine for 4 weeks. Angiogram pre & after procedure & at 6 months. Total follow-up 12 months</p>	<p><u>Primary clinical end point</u> <u>In hospital</u> – 1 radiation pts and 1 controlled pt had MI. <u>6 months</u> target site late loss index: Study pts: 11+/-36% Controls: 55+/-30% Late loss index similar in stented & balloon dilatation pts & across all 3 study gps. Restenosis rate: 8% in radiation pts vs 39% in controls Target lesion revascularization needed in 6% radiation pts & 24% controls. Restenosis of segments adjacent to target site – 11 in radiated pts and 3 in controls. <u>12 months</u> major adverse clinical events (death, MI or revascularization) in 16% of radiation pts and 24% study pts. 7 MI due to late thrombosis in radiated pts & no MI in controls (6/7 received a new stent at the procedure).</p>	<p>-Beta- radiotherapy with a centred (32)P source is safe and highly effective in inhibiting restenosis at the target site after stent or balloon dilatation. -Stenosis at the edge of the target site and unexpected late coronary thrombo-occlusive events were identified. Minimizing these must be accomplished to maximize the clinical benefit of this modality.</p>	<p>Level 2</p> <p>Prospective, double blinded, multicentre randomized sham-controlled study with large sample 12 month duration</p> <p>Control group much smaller than the total of the study gps.</p>
<p>Leon, MB et al Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. N Engl J Med 2001 Jan 25; 344(4):250-6</p> <p>(Gamma-I)</p> <p>(USA)</p>	<p>252 eligible patients who have developed in-stent restenosis, 131 randomized to receive ribbon with I-192 and 121 to the controlled group receive non-radioactive ribbon (placebo) 9 month follow up on survival, MI and need for repeated revascularization</p>	<p>37/131 of the radiation gp vs 53/121 of the controlled group suffered the composite end point of death, MI or revascularization.</p> <p>Reduction in incidence mainly due to decreased need for revascularization and not due to death or MI.</p> <p>Late thrombosis occurred in 5.3% of the I-192 group as compared with 0.8% of the placebo group</p>	<p>Intra-coronary irradiation with I – 192 resulted in lower rates of clinical and angiographic restenosis although it was also associated with a higher rate of late thrombosis, resulting in an increased risk of MI. If the problem of late thrombosis can be overcome, IC irradiation with I-192 may become a useful approach to the treatment of in-stent restenosis.</p>	<p>Level 1</p> <p>Prospective, triple blind, randomized controlled trial with large sample. Duration 9 months</p>

Study (Reference)	Method	Results	Conclusion	Level of Evidence
<p>Ahmed JM et al Safety of intracoronary gamma-radiation on uninjured reference segments during the first 6 months after the treatment of in-stent restenosis a serial intravascular ultrasound study. Circulation 2000 May 16;101(19):2227-30</p>	<p>Identified 38 pts from the WRIST study that have the radiation or placebo source extended >10 mm proximal and distal to the in-stent restenosis lesion. 19 pts from the radiation gp 19 pts from the placebo gp. Serial external elastic membrane, (EEM) lumen and plaque and media areas were measured using intravascular ultrasound every 1 mm over 5 mm-long reference segments that were 6-10 mm proximal & distal to the in-stent stenosis lesion (to ensure that only the uninjured reference segment was analyzed).</p>	<p><u>@ 6 months During follow up</u> A similar small increase occurred in the plaque and media area in the proximal and distal reference segments in both the radiation and placebo patients. In the radiation pts, an increase in both the proximal & distal (EEM) area occurred; as a result, no change in lumen area occurred. In the placebo patients, the proximal reference EEM area decreased and no change occurred in the distal reference EEM area contributing to a decrease in lumen area.</p>	<p>There was no evidence of a deleterious effect of gamma irradiation on angiographically normal uninjured reference segments in the first 6 months after treatment of in-stent restenosis.</p>	<p>Level 2I Prospective randomized study with small sample.</p>
<p>Meerkin D et al Effects of Intra-coronary B-radiation therapy after coronary angioplasty. Circulation 1999 Apr; 99(13): 1660-5 Canada (Montreal Heart Institute)</p>	<p>After successful balloon dilatation, 30 pts were randomized to receive 12, 14 or 16 Gy beta-radiation @ 2 mm from the center of the radiation source. The radiation source is seed trains with ⁹⁰ Strontium encapsulated and delivered via a non-centered catheter. Pts received monthly telephone follow-up, clinical follow-up @ 3 months and coronary angiography & intravascular ultrasound @ 6 months.</p>	<p>4 pts required stents in the first week. 3/30 pts – binary angiographic restenosis target lesion revascularization in 3/30 pts target vessel revascularization in 5/30 pts Angiographic late loss=0.02+/-0.6 mm No significant reduction in lumen areas. No significant change in external elastic membrane area over the 6 months follow-up. No significant difference among the dose groups</p>	<p>Beta radiation therapy resulted in low restenosis rate with negligible late loss by angiography. By intravascular ultrasound, beta radiation was shown to inhibit neointimal formation with no reduction of total vessel area at 6 month follow-up.</p>	<p>Level 4c Prospective non-controlled randomized trial for varying radiation doses. Small sample.</p>
<p>Kozuma K et al Relationship between tensile stress and plaque growth after balloon angioplasty treated with and without intracoronary beta brachytherapy Eur Heart J 2000 Dec;21(24):2063-70 The Netherlands</p>	<p>Of 31 consecutive patients successfully treated with balloon dilatation, 18 were randomized to receive catheter-based beta-radiation and 13 to the control group. 2 mm segments of the vessel were analyzed qualitatively & quantitatively by 3-D intravascular ultrasound post procedure and follow-up. Tensile stress was calculated.</p>	<p>Plaque growth was positively correlated to tensile stress in both groups. Low-dose sub-segments had a significant correlation whereas no correlation was observed in the effective dose. Tensile stress was shown to be the only independent predictor of plaque increase in non-irradiated sub-segments whereas actual dose and plaque morphology were stronger predictors in irradiated sub-segments.</p>	<p>Results suggest that plaque growth is related to tensile stress after balloon dilatation. Intracoronary brachytherapy may alter the biophysical process on plaque growth when the prescribed dose is effectively delivered.</p>	<p>Level 2 Randomized controlled study Small sample size</p>

Study (Reference)	Method	Results	Conclusion	Level of Evidence
<p>Schuhlen H, et al Usefulness of intracoronary brachytherapy for in-stent restenosis with a 188 Re liquid-filled balloon Am J Cardiol 2001 Feb 15; 87(4):463-6, A7</p> <p>(Germany)</p>	<p>21 patients: 11 randomized to receive intracoronary radiation & 10 controls. Radiation source: a rhenium-188 liquid-filled balloon system to prevent recurrent restenosis after percutaneous transluminal coronary balloon dilatation for in-stent restenosis</p>	<p>4 pts in radiation gp received additional stent @ 6 months: 1 pt from radiation gp and 6 controls returned with recurrent symptoms @ 1 year, significant angiographic indexes of restenosis in rad. Pts. 3/11 radiation pts vs 8/10 controls needed repeat balloon dilatation.</p>	<p>Intra-coronary brachytherapy can be administered safely with a 188 Re liquid-filled balloon system.</p>	<p>Level 2 Prosp. randomized controlled trial with Small sample size. Included because it describes a liquid-filled balloon system to deliver the radiation.</p>
<p>Waksman R et al Late total occlusion after intracoronary brachytherapy for patients with in-stent restenosis. J Am Coll Cardiol 2000 Jul;36(1):65-8</p> <p>USA</p>	<p>Reviewed records of 473 patients presented with in-stent restenosis. 308 pts randomized to received gamma or beta radiation and 165 received placebo. Dosage or radiation varied 30-55Gy. All received anti-platelet therapy. All completed at least 6 mos angiography FU.</p>	<p>Late total occlusion documented in 9.1 % of irradiated gp vs 1.2% of placebo gp. In the irradiated gp, late total occlusion [LTO] presented as acute MI in 43%, unstable angina in 50% and asymptotic in 7%. Restenting placed in 82% of the irradiated and in 100% of the placebo pt with LTO.</p>	<p>Intracoronary radiation for patients with in-stent restenosis is associated with a high rate of LTO. Restenting may contribute to late thrombosis. Prolonged anti-platelet therapy should be considered for these patients.</p>	<p>Level 2 Retrospective review of multiple RCT. Study subjects received different type of radiation and probably different study protocols.</p>
<p>Waksman R 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 May; 103(19):2332-5</p> <p>USA</p>	<p>120 consecutive pts with diffuse in- stent restenosis in native coronary arteries and vein grafts underwent percutaneous balloon dilatation, laser ablation and/or rotational atherectomy. 34 pts (28.3%) received additional stents. All patients received intracoronary gamma radiation of the treated sites from (192)Ir concealed in ribbons (a dose of 14 Gy to 2 mm) Pts were placed on clopidogrel and aspirin for 6 months & followed angiographically & clinically. The late occlusion & thrombosis rate were compared to the gamma-radiation treated (n=125) & the placebo pts (125) in the WRIST trials.</p>	<p>Only 1 pt did not tolerate clopidogrel At 6 months: Gp with prolonged anti-platelet therapy had a total occlusion rate of 5.8% and a late thrombosis rate of 2.5%; These rates were lower than those in the active gamma-radiation group and similar to the placebo control gp in the Wrist trials.</p>	<p>Six months of clopidogrel and aspirin and a reduction in restenting for patients with in-stent restenosis treated with gamma-radiation is well tolerated and associated with a reduction in the late thrombosis rate compared with a similar cohort treated with only 1 month of clopidogrel and aspirin.</p>	<p>Level 3b Prospective study with a large sample with a historical placebo and treatment group for comparison.</p>

Study (Reference)	Method	Results	Conclusion	Level of Evidence
Shiran A et al Early lumen loss after treatment of in-stent restenosis: an intravascular ultrasound study Circulation 1998 Jul 21;98(3):200-3	37 lesions in 36 pts previously treated with stents 8 received percutaneous transluminal angioplasty (PTCA), 12 received excimer laser coronary balloon dilatation+ adjunct PTCA, 17 received rotational atherectomy + adjunct PTCA <u>After intervention, pts were randomized into two gps:</u> 27 lesions received gamma radiation from a nylon ribbon with 192-I, 15 Gy at 2 mm) 10 lesions(received placebo ribbon Intravascular ultrasound was performed before and after procedure.	The study has not yet been unblinded, the impact of radiation vs placebo cannot be determined. Result: Stent volume increased initially in the radiation gp. After a delay of (42+/-8 min), minimal lumen area decreased by 20% and the lumen volume decreased by 12%. 27% of had a > or = 2.0 mm2 decrease in minimal lumen area. Lumen loss (1) resulted from increased tissue in the stent; (2) correlated with lesion length and preintervention in-stent tissue and (3) was not seen angiographically.	There is a significant tissue reintrusion shortly after catheter based treatment of in-stent restenosis. This was greater in longer lesions and those with a larger in-stent tissue burden and was not reflected in the qualitative coronary angiography.	Level 2 Prospective randomized, double-blind, controlled trial study No comparison results reported because the study has not yet been un-blinded.
Verin V et al Endoluminal beta-radiation therapy for the prevention of coronary restenosis after balloon angioplasty. The Dose-Finding Study Group N Engl J Med 2001 Jan 25; 344(4): 243-9 (Geneva)	After successful balloon dilatation of previously untreated coronary stenosis: 181 patients randomly assigned to receive 9, 12, 15 or 18 Gy of radiation from Yttrium-90 source. Adjunct stenting required in 28% of patients. Monitor luminal diameter at 6 months following treatment.	86% had no serious cardiac event. 6 month luminal diameter: 1.67mm(9 Gy), 1.76mm(12-Gy), 1.83mm (15-Gy) and 1.97mm(18-Gy). Restenosis rate: 29% (9-Gy)	Intra-coronary beta radiation therapy produces a significant dose-dependent decrease in the rate of restenosis after balloon dilatation. An 18-Gy dose not only prevents the re-narrowing of the lumen but actually induces luminal enlargement	Level 4c Prospective trial to test dose-response effect of intracoronary radiation.
Costa MA et al Late Coronary Occlusion After Intracoronary Brachytherapy Circulation 1999 Aug 24;100(8):789-92 The Netherlands	108 consecutive patients were successfully treated with catheter-based intracoronary beta-radiation . The Beta-Cath system was used in 76 pts (32 stents, 44 balloon angioplasty) The Guidant intravascular brachytherapy system was used in 32 pts (13 stents and 19 balloon dilatation) Intravascular ultrasound & angiography were performed after the procedure & @ 6 month follow-up.	<u>At six month follow-up:</u> 6.6% of the pts suffered sudden thrombotic events 2-15 months after radiation.	Late and sudden thrombosis after PTCA followed by intracoronary radiotherapy is a new phenomenon in interventional cardiology. The effect of radiation on delaying the healing process and maintaining a thrombogenic coronary surface is proposed as the most plausible mechanism to explain such late events.	Level 4c Non-randomized case series.

Study (Reference)	Method	Results	Conclusion	Level of Evidence
<p>Silber S et al Safety and feasibility of intracoronary brachytherapy with the Novoste system within the scope of international multicenter studies. Z Kardiol 2000 Apr;89(4):323-9 (English abstract) Germany</p>	<p>92 pts (104 lesions) within the international multicenter studies BETA-CATH, START and BRIE received intracoronary brachytherapy via the Novoste system (beta radiation delivered via a catheter) The mean applied radiation dose was 16+/-2 GY at 2 mm distance. All pts received ASS 300 mg/d o.d. Patients with stent implantation in the same session received 250 mg Ticlopidine or 75 mg Clopidogrel for at least 3 months.</p>	<p>Total mortality and infarct rate=0 There was no acute, subacute or late stent thrombosis.</p>	<p>The first experience with the Novoste Beta-Cath system showed that intracoronary brachytherapy can be safely and simply performed in the cath lab. There were no acute complications. To avoid the possible risk of late stent thrombosis, Ticlopidine or Clopidogrel must be administered for at least three months.</p>	<p>Level 4b Non-randomized multicentre case series.</p>
<p>Raizner AE et al Clinical experience with a spiral balloon centering catheter for the delivery of intracoronary radiation therapy Cardiovasc Radiat Med 1999 Jul-Sep; 1(3):214-9 USA</p>	<p>In 3 clinical trials, radiation or placebo was delivered to 312 pts using the Galileo Centering Catheter – a spiral balloon allows centering and facilitates perfusion to the distal artery and side branches. The catheter contains a dedicated dead-end lumen for source wire delivery to the lesion site.</p>	<p>The delivery (radiation or placebo) was successful in 300 of 312 pts (96%). With balloon inflation, grade 2 or 3 flow was achieved in side branches in 82% and in the distal artery in 77% of pts</p>	<p>The Galileo Centering Catheter is a safe and highly effective method for delivering intracoronary radiation therapy.</p>	<p>No comparative results reported. Only reported on the success rate of delivering the radiation.</p>
<p>Sianos G et al Geographical miss during catheter-based intracoronary beta-radiation: incidence and implications in the BRIE study. Beta Radiation in Europe. J Am Coll Cardiol 2001 Aug;38(2):415-20</p>	<p>175 vessels treated by beta-radiation in the BRIE study were analyzed. The effective irradiated segment and both edges were studied with quantitative coronary angiography. Restenosis defined as diameter stenosis >50% at follow up Geographical miss determined by simultaneous electrocardiographic-matched, side-by-side projection of the source and balloons deflated at the injury site.</p>	<p>Geographical miss affected 41.2% of the edges Restenosis rate in geographical miss edges = 16.3 %. Increased in both proximal and distal edges. Restenosis rate in non-geographical miss edges = 4.3% Geographical miss associated with stent injury significantly increased edge stenosis. Geographical miss related to balloon injury did not significantly increase edge stenosis.</p>	<p>Geographical miss is strongly associated with restenosis at the edges of the effective irradiated segment.</p>	<p>Retrospective analysis of data obtained from a prospective multicentre trial.</p>

Study (Reference)	Method	Results	Conclusion	Level of Evidence
Latchem DR et al Beta-radiation for coronary in-stent restenosis Catheter Cardiovasc Interv 2000 Dec;51(4):422-9 Switzerland	37 pts treated with beta radiation after balloon dilatation. Radiation source – 30 mmm strontium 90 The mean reference diameter was 2.9+/-0.5mm 62% of lesions were diffuse including 4 total occlusions. Follow-up 7.1+/-4.5 months. Restenosis defined as diameter stenosis >50%	Beta radiation was successfully delivered in 36 pts (97%) During the follow-up period: No MI 3 deaths (1 preexisting cancer, 1 from progressive cardiac failure, 1 from sudden cardiac death) Target vessel revascularization in 7/36 pts (19%) 6 month angiography in 30 pts showed: restenosis in 10% of pts edge stenosis in 13% late (> 1 month) thrombotic occlusion in 7%	Beta-radiation for in-stent restenosis is associated with encouragingly low rates of target lesion restenosis and target vessel restenosis. Further improvements are needed to solve the limitations of the edge effect and late occlusion.	Level 4c Case series with small sample.
Meerkin D et al The effects of intracoronary brachytherapy on the natural history of postangioplasty dissections J Am Coll Cardiol 2000 Jul;36(1):59-64 Canada	94 patients from intravascular ultrasound sub-study of the MultiVitamins & Probuic (MVP) trial and 26 non-stented patients in the Beta Energy Restenosis Trial (BERT) were analyzed for the presence or absence of dissection.	Of the 28 pts with postangioplasty dissections in the MVP, only one had evidence of residual dissection at 6 months. 9 of 16 dissections had healed in BERT subjects. Improvement in irradiated pts was demonstrated. They showed significant increase in lumen area at 6 months. In both groups, the external elastic membrane area was unchanged at follow-up.	Resolution appears to be the natural history of intravascular ultrasound –detected dissections in most cases. Significant resolution of dissection occurs following intracoronary beta-radiation as reflected in reduced dissection at six months although significant impairment of vessel wall healing was noted.	Level 4c Non-randomized retrospective study on pts drawn from two randomized trials..
Hoher M et al Intracoronary B-Irradiation with a Liquid 188-Re-filled Balloon. Six-month results from a clinical safety and feasibility study. Circulation 2000;101(20):2355	N = 28 patients including 19 de novo stenosis and 4 occlusions and 5 restenosis. 9 underwent balloon dilatation and 19 with stenting. All lesions received beta radiation from a liquid 188-Re filled angioplasty balloon and received 15 Gy at 0.5mm tissue depth. Clinical follow-up was performed after 3 months and angiographic follow-up after 6 months.	@ 6 months, minimal lumen diameter was 1.45+/-0.88 mm with late loss index 0.57. Target lesion restenosis rate 12%; 9 stenosis at the proximal or distal end of the irradiation zone (edge stenosis). Total restenosis rate was 46% and was 29% vs 70% when the length of the irradiated segment was more than 2x the lesion length.	Coronary irradiation with 188-RE-filled balloon is technically feasible and safe, requiring only standard percutaneous transluminal coronary angioplasty techniques. The target lesion stenosis rate was low. The observed edge stenoses appear to be avoidable by increasing the length of the irradiated section	Level 4c

Study (Reference)	Method	Results	Conclusion	Level of Evidence
<p>Albiero R. Short and Intermediate-Term Results of 32-P Radioactive B-emitting Stent Implantation in Patients with Coronary Artery Disease. The Milan Dose-Response Study Circulation 2000;101(18):</p>	<p>82 patients with 91 lesions received beta-radiation from 122 32-P B-emitting stents.</p> <p>The patients all received 0.75 uCi from one type of stent and then divided into three groups Gp 1, n=23 pts received 0.75-3.uCi Gp 2, n=30pts received 3.0-6 uCi Gp 3 (n=30 pts) received 6 – 12.0 Ci</p> <p>Patients were followed for 6 months</p>	<p>There were no procedural events. At 6 months:</p> <p>There were no deaths 1 stent thrombosis. Pure intrastent binary stenosis: 16% in gp 1 3% in gp 2 0% in Gp 3. Intrastent restenosis was 52% in gp 1, 41% in gp 2 and 40% in Gp 3.</p>	<p>The use of 32P radioactive B-emitting stents in patients with CAD is feasible. However, in the 3 groups, intrastent restenosis was high because of a high late lumen loss in the reference segments at the stent edges, possibly as a result of a low activity level of radiation at the edges of the stent combined with an aggressive approach to stenting.</p>	<p>Level 4c</p> <p>Large prospective study on dose effect.</p>
<p>Kay IP et al Radioactive Stents Delay but do not prevent in-stent neointimal hyperplasia. Circulation 2001;103:14</p> <p>De novo lesions</p>	<p>Part of the European 32-P Dose Response Trial N=40 patients undergoing initial stent implantation received beta emitting 32-P coated radioactive stents that delivered 6-12 uCi .</p> <p>Patients were followed up for one year using serial quantitative angiography and volumetric ECG-gated 3D intravascular ultrasound.</p>	<p>Significant luminal deterioration was observed within the stents between 6 months and 1 year as demonstrated by a decrease in the angiographic minimum lumen diameter of 0.43+/-0.56 mm and in the mean lumen diameter of the stent (-0.55 +/-0.63mm). A significant increase in in-stent neointimal hyperplasia by IVUS TVR was performed in 23% of pts. No late occlusion, MI or death 65% remained event free at one year</p>	<p>Neointimal proliferation is delayed rather than prevented by radioactive stent implantation. Clinical outcome at one year after implantation of stents with an initial activity of 6-12 uCi is not favorable when compared with conventional stenting.</p>	<p>Non-randomized Case</p> <p>Level 4c</p>
<p>Wardeh AJ et al B-Particle-Emitting Radioactive Stent Implantation: A safety and Feasibility Study. Circulation 1999; 100:1684-1689</p> <p>The Netherlands</p>	<p>Part of the Isostents for Restenosis Intervention Study 31 radioactive 32-P coated stents were implanted in 26 patients. The stents were to deliver 0.75 – 1.5 u Ci to the lesions over 100 days. Quantitative coronary angiography measurements were performed before and after the procedure and at 6 months follow-up. All patients received aspirin indefinitely and ticlopidine for 4 weeks.</p>	<p>Five patients received additional non-radioactive stents. Placement of radioactive stents had a success rate of 97%. 23 patients (88%) returned for follow-up Average treated lesion length =13+/-4mm Minimum lumen diameter increased from 0.87+/-0.28mm to 2.84+/-0.35mm post irradiation. No in hospital adverse cardiac events. @ 6 months; 17 had in-stent stenosis, 13 had revascularization. No edge stenosis observed. Late loss of lumen diameter of 0.99+/-0.89mm, late loss index of 0.53.</p>	<p>The use of radioactive stents with an activity of 0.75 to 1.5 uCi is safe and feasible.</p> <p>Problem: Detecting an embolized radioactive stent is a problem.</p> <p>Results similar to non- radioactive stents.</p> <p>Particular attention was paid to avoiding balloon injury to prevent edge effects.</p>	<p>multicentre trial Case series</p> <p>Level 4b</p>

Study (Reference)	Method	Results	Conclusion	Level of Evidence
Parikh SK et al Practical considerations in setting up an intracoronary brachytherapy program: results of a multicenter survey Radiology 2000 Dec;217(3):723-8 (USA)	Radiation oncologist from 12 sites that have participated in double blind RCT of intracoronary radiation therapy completed a questionnaire regarding demographics, experience, regulatory issues, scheduling, interaction with patients, time commitment and involvement etc.	Questionnaire identified several issues: <ul style="list-style-type: none"> • Licensing perceived as a substantial hurdle, some took more than 5 mos. • 75% radiation oncologists did not see pts prior to the procedures & not involved in obtaining informed consent. • Mean time spent with pts 30-90minuts 	<ul style="list-style-type: none"> • Issues identified need to be addressed before intracoronary RT becomes a part of widespread clinical practice. • Close collaboration between cardiologists & radiation oncologists at various levels is required to ensure that the patient derive maximal benefit from the new technology. 	Observational studies Level 4b

**APPENDIX V: Perspectives (Guidelines) of the American Brachytherapy Society
(published 1999)**

- Intravascular brachytherapy (IVB) is still experimental, the long-term efficacy, toxicity, target tissue & dose required have not been established.
- IVB procedures must be performed with careful attention to radiation-related issues, in the context of controlled multidisciplinary clinical trials, with the approval of the institutional review board, the Nuclear Regulatory Commission, the FDA, and under an Investigational Device Exemption.
- The therapeutic radiologist with a qualified radiation physicist is responsible for dose prescription and delivery, and needs to be present during the IVB procedure as part of this multidisciplinary team.
- These studies should be critically reviewed & published in peer-reviewed journals.
- Dosimetric guidelines of the American Association of physicists in Medicine Task Group 60 are endorsed.
- Dose specification should be defined clearly to allow comparisons between studies.
- The dose should be prescribed at 2 mm from the source for intracoronary brachytherapy, and at an average luminal radius of + 2 mm for peripheral to determine the long-term outcome from vascular brachytherapy.
- Comprehensive procedures for quality QA, radiation protection, and emergencies should be in place before initiating an IVB program.
- Long-term outcome data with a standardized reporting system are needed to establish the role of brachytherapy in preventing vascular stenosis. Endovascular brachytherapy is a new and evolving modality and the recommendations are subject to modifications, as new data become available.

REFERENCES

1. Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C. Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review. NHS R&D HTA Program. Health Technology Assessment 2000; 4(23)
2. Sapirstein W., Zuckerman B, Dillard J. FDA Approval of Coronary Artery Brachytherapy. N Engl J Med 2001 Jan;344(4):297-299.
3. Mintz GS, Weissman NJ, Teirstein PS, Ellis SG, Waksman R, Russo RJ, Moussa I, Tripuraneni P, Jani S, Kobayashi Y, Giorgianni JA, Pappas C, Kuntz RA, Moses J, Leon MB. Effect of intracoronary gamma-radiation therapy on in-stent restenosis: An intravascular ultrasound analysis from the gamma-1 study. Circulation. 2000 Dec 12;102(24):2915-8.
4. CCN Expert Panel on Intracoronary Stents Final Recommendations (January 1997), Cardiac Care Network of Ontario.
5. Leon MB, Teirstein PS, Moses JW, Tripuraneni P, Lansky AJ, Jani S, Wong SC, Fish D, Ellis S, Holmes DR, Kerieakes D, Kuntz RE. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. N Engl J Med. 2001 Jan 25;344(4):250-6.
6. Raizner AE, Oesterle SN, Waksman R, Serruys PW, Colombo A, Lim YL, Yeung AC, van der Giessen WJ, Vandertie L, Chiu JK, White LR, Fitzgerald PJ, Kaluza GL, Ali NM. Inhibition of restenosis with beta-emitting radiotherapy: Report of the Proliferation Reduction with Vascular Energy Trial (PREVENT). Circulation. 2000 Aug 29;102(9):951-8.
7. Waksman R, Ajani AE, White RL, Pinnow E, Mehran R, Bui AB, Deible R, Gruberg L, Mintz GS, Satler LF, Pichard AD, Kent KM, Lindsay J. Two-year follow-up after beta and gamma intracoronary radiation therapy for patients with diffuse in-stent restenosis. Am J Cardiol. 2001 Aug 15;88(4):425.
8. Waksman R, Bhargava B, White L, Chan RC, Mehran R, Lansky AJ, Mintz GS, Satler LF, Pichard AD, Leon MB, Kent KK. Intracoronary beta-radiation therapy inhibits recurrence of in-stent restenosis. Circulation 2000 Apr 25;101(16):1895-8.
9. Teirstein PS, Massullo V, Jani S, Popma JJ, Russo RJ, Schatz RA, Guarneri EM, Steuterman S, Sirkin K, Cloutier DA, Leon MB, Tripuraneni P. Three-year clinical and angiographic follow-up after intracoronary radiation: results of a randomized clinical trial. Circulation. 2000 Feb 1;101(4):360-5.
10. Waksman R, Bhargava B, White L, Chan R, Gierlach L, Mehran R, Lansky A, Kent K, Mintz G, Satler L, Pichard A, Leon M. Intracoronary Radiation for Patients with Refractory In-Stent Restenosis: An analysis from the WRIST-Crossover Trial. Cardiovasc Radiat Med.1999;1(4):317-322.
11. Waksman R, White RL, Chan RC, Bass BG, Geirlach L, Mintz GS, Satler LF, Mehran R, Serruys PW, Lansky AJ, Fitzgerald P, Bhargava B, Kent KM, Pichard AD, Leon MB. Intra-Coronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. Circulation 2000 May;101(18):2165-71.

12. Ahmed JM, Mintz GS, Waksman R, Mehran R, Leiboff B, Pichard AD, Satler LF, Kent KM, Weissman NJ. Serial intravascular ultrasound assessment of the efficacy of intracoronary gamma-radiation therapy for preventing recurrence in very long, diffuse, in-stent restenosis lesions. *Circulation*. 2001 Aug 21;104(8):856-9.
13. Meerkin D, Tardif JC, Crocker IR, Arsenault A, Joyal M, Lucier G, King SB 3rd, Williams DO, Serruys PW, Bonan R. Effects of intracoronary beta-radiation therapy after coronary angioplasty: an intravascular ultrasound study. *Circulation*. 1999 Apr 6;99(13):1660-5.
14. Kozuma K, Costa MA, Sabate M, Slager CJ, Boersma E, Kay IP, Marijnissen JP, Carlier SG, Wentzel JJ, Thury A, Ligthart JM, Coen VL, Levendag PC, Serruys PW. Relationship between tensile stress and plaque growth after balloon angioplasty treated with and without intracoronary beta-brachytherapy. *Eur Heart J*. 2000 Dec;21(24):2063-70.
15. King SB, Williams DO, Chougule P, Klein JL, Waksman R, Hilstead R, Macdonald J, Anderberg K, Crocker IR. Endovascular b-radiation to reduce restenosis after coronary balloon angioplasty. Results of the Beta Energy Restenosis Trial (BERT). *Circulation* 1998; 97:2025-2030.
16. Hoher M, Wohrle J, Wohlfrom M, Hanke H, Voisard R, Osterhues HH, Kochs M, Reske SN, Hombach V, Kotzerke J. Intracoronary beta-irradiation with a liquid (188)re-filled balloon: six-month results from a clinical safety and feasibility study. *Circulation*. 2000 May 23;101(20):2355-60.
17. Albiero R, Adamian M, Kobayashi N, Amato A, Vagheti M, Di Mario C, Colombo A. Short- and intermediate-term results of (32)P radioactive beta-emitting stent implantation in patients with coronary artery disease: The Milan Dose-Response Study. *Circulation*. 2000 Jan 4-11;101(1):18-26.
18. Kay IP, Wardeh AJ, Kozuma K, Foley DP, Knook AH, Thury A, Sianos G, van der Giessen WJ, Levendag PC, Serruys PW. Radioactive stents delay but do not prevent in-stent neointimal hyperplasia. *Circulation*. 2001 Jan 2;103(1):14-7.
19. Wardeh AJ, Kay IP, Sabate M, Coen VL, Gijzel AL, Ligthart JM, den Boer A, Levendag PC, van Der Giessen WJ, Serruys PW. beta-Particle-emitting radioactive stent implantation. A safety and feasibility study. *Circulation*. 1999 Oct 19;100(16):1684-9
20. Shiran A, Mintz GS, Waksman R, Mehran R, Abizaid A, Kent KM, Pichard AD, Satler LF, Popma JJ, Leon MB. Early lumen loss after treatment of in-stent restenosis: an intravascular ultrasound study. *Circulation*. 1998 Jul 21;98(3):200-3.
21. Latchem DR, Urban P, Goy JJ, De Benedetti E, Pica A, Coucke P, Eeckhout E. Beta-radiation for coronary in-stent restenosis. *Catheter Cardiovasc Interv*. 2000 Dec;51(4):422-9.
22. Sianos G, Kay IP, Costa MA, Regar E, Kozuma K, de Feyter PJ, Boersma E, Disco C, Serruys PW. Geographical miss during catheter-based intracoronary beta-radiation: incidence and implications in the BRIE study. *Beta-Radiation In Europe*. *J Am Coll Cardiol*. 2001 Aug;38(2):415-20.

23. Parikh S, Nori D, Tripuraneni P. Geographic miss: a cause of treatment failure in radio-oncology applied to intracoronary radiation therapy. *Circulation*. 2001 Mar 27;103(12):E65
24. Kim HS, Waksman R, Cottin Y, Kollum M, Bhargava B, Mehran R, Chan RC, Mintz GS. Edge stenosis and geographical miss following intracoronary gamma radiation therapy for in-stent restenosis. *J Am Coll Cardiol*. 2001 Mar 15;37(4):1026-30.
25. Waksman R, Bhargava B, Leon MB. Late thrombosis following intracoronary brachytherapy. *Catheter Cardiovasc Interv*. 2000 Mar;49(3):344-7.
26. Waksman R, Ajani AE, White RL, Pinnow E, Dieble R, Bui AB, Taaffe M, Gruberg L, Mintz GS, Satler LF, Pichard AD, Kent KK, Lindsay J. 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 May ;103(19):2332-5.
27. Costa MA, Sabat M, van der Giessen WJ, Kay IP, Cervinka P, Ligthart JM, Serrano P, Coen VL, Levendag PC, Serruys PW. Late coronary occlusion after intracoronary brachytherapy. *Circulation*. 1999 Aug 24;100(8):789-92.
28. Verin V, Popowski Y, de Bruyne B, Baumgart D, Sauerwein W, Lins M, Kovacs G, Thomas M, Calman F, Disco C, Serruys PW, Wijns W. Endoluminal beta-radiation therapy for the prevention of coronary restenosis after balloon angioplasty. The Dose-Finding Study Group. *N Engl J Med*. 2001 Jan 25;344(4):243-9.
29. Parikh SK, Dattatreya N, Osian A, Tripuraneni P. Practical Considerations in Setting Up an Intracoronary Brachytherapy Program Results of a Multicenter Survey. *Radiology*. 2000;217:723-728.
30. Fischell TA. New Data, New Era With Drug-Eluting Stents, American Heart Association Scientific Sessions, November, 2001.
31. Schnyder G, Rpfpo M, Pin R, Flammer Y, Lange H, Eberli F, Meier B, Turi G, Hess O. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. *N Engl J Med* 2001 Nov;345(29):1593-1600.

Review Articles used for background information

32. Gruberg L, Waksman R. Intravascular radiation for the prevention of recurrence of restenosis in coronary arteries. *Expert Opin Investig Drugs*. 2001 May;10(5):891-907. Review.
33. Morris NB. Brachytherapy. Savior or tease. *Crit Care Nurs Clin North Am*. 1999 Sep;11(3):333-48. Review.
34. Sheppard R, Eisenberg MJ. Intracoronary radiotherapy for restenosis. *N Engl J Med*. 2001 Jan 25;344(4):295-7.
35. Gruberg L, Waksman R, Satler LF, Pichard AD, Kent KM. Novel approaches for the prevention of restenosis. *Expert Opin Investig Drugs*. 2000 Nov;9(11):2555-78. Review.

36. Nag S, Cole PE, Crocker I, Jani SK, Kishnasastry KV, Massullo V, Nath R, Nori D, Parikh S, Rubin P, Speiser B, Teirstein PS, Tripuraneni P, Waksman R, Williamson JF. The American Brachytherapy Society perspective on intravascular brachytherapy. *Cardiovasc Radiat Med.* 1999 Jan-Mar;1(1):8-19. Review.
37. Intracoronary radiation therapy for restenosis prevention: status of the clinical trials. *Cardiovasc Radiat Med.* 1999 Jan-Mar;1(1):20-9. Review.
38. Salame M, Douglas J. The Restenosis Story: Is Intracoronary Radiation Therapy the Solution? *Cardiology in Review* 2001;8(6):329-338.
39. Popma J. Stents and radiation therapy. Presented at the American College of Cardiology Scientific Session, Anaheim, CA, March 2000. <http://www.acc.org/education/online/trials>
40. Goodman,C. Literature searching and evidence interpretation for assessing health care practices. Stockholm: SBU. Swedish Council on Technology Assessment in Health Care; 1993.