The introduction of intracoronary stents has dramatically improved the safety of angioplasty, expanded the type of patients that can be treated percutaneously, and reduced the need for repeat intervention due to restenosis. However, it has not cured the problem of restenosis. While stents reduce the rate of restenosis by inhibiting vessel recoil and late negative remodeling by scaffolding the vessel, they also elicit a foreign body tissue response leading to neointimal proliferation. In approximately 15–20% of patients, this is severe enough to result in in-stent restenosis. When conventional interventional techniques, including repeat balloon angioplasty (PTCA), re-stenting, laser therapy or atherectomy are used to treat this problem, the recurrence rate is high (19–83%).

Efficacy of intravascular brachytherapy for in-stent restenosis. Radiation therapy is known to be effective in the treatment of other benign hyperproliferative disorders (e.g., keloids, pterygia). Therefore, its use to treat another benign, hyperproliferative condition — neointimal hyperplasia — was logical. The largest body of data from randomized, placebo-controlled trials in man relate to the use of gamma radiation with Iridium-192 for the treatment of severe in-stent restenosis. These studies show marked, concordant evidence of efficacy by quantitative coronary angiography, intravascular ultrasound and clinical criteria in a patient population with a very high rate of recurrence when treated by conventional means. Furthermore, the efficacy appears to be sustained long-term.

Safety concerns with intravascular brachytherapy for in-stent restenosis

There are currently two main concerns about the use of intravascular brachytherapy for the treatment of in-stent restenosis: 1) risk of late thrombosis/late total occlusion; and 2) radiation risk to the patient and the staff.

Late stent thrombosis/total occlusion. Thrombus formation is a well-known risk of both simple balloon angioplasty (when it usually occurs within the first 24 hours) and stenting (when it tends to occur in the first few days following stenting). These subacute thromboses (SATs) occur because of the exposure of bare metal to the bloodstream prior to endothelialization of the stent, which typically takes 2–6 weeks. The risk of SATs can be minimized by ensuring good application of the stent to the arterial wall and by continuing dual antiplatelet therapy with aspirin and a thienopyridine (ticlopidine or clopidogrel) for 2–4 weeks.

In patients treated with intravascular brachytherapy for in-stent restenosis, “late stent thrombosis” (LST) has been observed to occur well beyond 30 days. This was first observed in trials involving a Sr-90/Y-90 beta radiation source and was subsequently also seen in the Ir-192 gamma radiation trials. The cause of this phenomenon is believed to be delayed endothelialization of a newly placed stent and insufficient duration of antiplatelet therapy. Assessment of the frequency of this phenomenon has been complicated by lack of a consistent definition. Kuntz has therefore proposed use of the following terms and definitions:

- Symptomatic Late Thrombosis (SLT): Thrombosis occurring more than 30 days post-procedure associated with symptoms and signs of an acute myocardial infarction, and confirmed angiographically.
• Late Total Occlusion (LTO): A vessel that is shown to be totally occluded (more than 30 days post-procedure) by angiography, whether clinically or protocol driven, with or without symptoms.
• Asymptomatic Late Occlusion: The difference between the LSO and SLT rates.

The SLT definition is clearly the most specific, but may potentially miss some occlusions. Conversely, the LTO definition overstates the frequency of thrombotic occlusions, since it encompasses both vessel closure due to thrombosis and hyperproliferation of the intima — the original problem. Using these definitions, the incidence of symptomatic late thrombosis (SLT) in the Gamma-I trial was 5.3% in the radiation group and 0.8% in the placebo group ($p = 0.06$), while the LTO rates were 13.5% and 5.8%, respectively ($p = 0.06$). A similar rate of SLTs was seen in the radiation-treated patients in the SCRIPPS I trial (60 patients) and WRIST trial (130 patients) (Table 1).

Because of the low absolute frequency of these events, data from the randomized gamma radiation trials were pooled. This showed that the problem was virtually confined to patients who were irradiated and received a new stent (6.7% incidence) versus 1.2% in irradiated patients who were not restented. This latter incidence was similar to the incidence of SLTs in patients who were not irradiated and received a new stent (0.7%) and those who were neither radiated nor re-stented (1.4%) (Figure 1).

In these trials, patients received dual antiplatelet therapy ranging from 2–8 weeks, and there was a very high rate of new stent placement (84% in GAMMA-I). Conversely, in the ongoing SCRIPPS III and WRIST PLUS trials, with 6-month dual antiplatelet therapy and a low usage of new stents (25%), there have been only 2 SLTs out of 307 patients who have had 6-months or longer follow-up. Thus, it seems that late thrombosis can be minimized and reduced to the rate seen in stented, non-irradiated vessels by minimizing the use of new stents at the time of brachytherapy and by extending dual antiplatelet therapy (with aspirin and a thienopyridine) for 6–12 months.7

Patient and staff safety. The CHECKMATE™ system has shown a high degree of efficacy and safety. In the GAMMA-I trial, the system performed exceptionally well. Specifically, in 252 patients at 12 sites there were:

- no device failures
- no procedural failures
- no cases in which the source was not delivered
- no cases in which a lead-lined bail-out box was used

The reason for these very satisfying results include: 1) a user-friendly 3.7 French rapid-exchange catheter; 2) integrity of the radioactive source wire; 3) simple mechanics; and 4) Ir-192 dwell-time of approximately 20 minutes allows precise placement, repositioning if necessary and much greater margin of safety in terms of dosimetry.

In this regard, it is worth noting that the Nuclear Regulatory Commission views a deviation of more than 10% from the prescribed dose to be a “recordable” event and a deviation of more than 20% to be an NRC “reportable” event. In over 1,000 cases in the USA in which the CHECKMATE™ (Cordis Corporation, Miami Lakes, Florida) system has been used, there has not been one NRC reportable event to date. This represents an unsurpassed record of safety.

The ease of use of the system is also a very important factor in the very good safety profile of the CHECKMATE system. Use of this system, like all brachytherapy systems in the catheterization laboratories, requires a team approach. The interventional cardiologist, radiation oncologist, and radiation physicist all play an important role. The CHECKMATE system’s simple ribbon advanced into a catheter approach lends itself well to a smooth transition between cardiologist and radiation oncologist.

The different radioisotopes that are being used in clinical trials (e.g., Ir-192, Sr-90/Y-90, P-32), differ substantially in their ability to penetrate tissues and

![Graph: Distribution of Late Thrombosis](Pooled Data: SCRIPPS, WRIST, and GAMMA-I trials)

![Percentage Chart: Radiation vs. Placebo](New Stent, No New Stent)

![Table 1: Incidence of symptomatic late thrombosis (> 30 days post-procedure)](IRT* Placebo Crossover)

<table>
<thead>
<tr>
<th>Trial</th>
<th>IRT (%)</th>
<th>Placebo (%)</th>
<th>Crossover (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCRIPPS I</td>
<td>3.4%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>WRIST</td>
<td>6.1%</td>
<td>3.8%</td>
<td>5.1%</td>
</tr>
<tr>
<td>GAMMA-I</td>
<td>5.3%</td>
<td>0.8%</td>
<td>—</td>
</tr>
</tbody>
</table>

*all IRT patients except 1 had a new stent placed
IRT = intravascular radiation therapy

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Specifically, Ir-192, a gamma-emitter, suffers relatively little attenuation as it passes through tissue. This shallow “dose-gradient” means that for any given dose of radiation administered to the media-adventitial border, a much lower dose of radiation is delivered to the luminal surface with Ir-192 than with P-32 or Sr-90/Y-90. There is also much greater dose homogeneity and less dosage attenuation through stent struts and calcified plaque with Ir-192 than with the beta sources. However, this difference in dose-gradient also implies that additional portable lead shields may be required to shield the catheterization laboratory personnel from gamma radiation, while beta-emitters (such as Sr-90/Y-90 and P-32) can be shielded using certain forms of plastic material. Thus, care must be taken when using Ir-192 that the necessary precautions (lead-shielding and vacating the room) are taken during the period of brachytherapy, whereas this is not necessary for beta radiation. However, if the appropriate precautions are observed, Ir-192 can be used very safely, as reported by Jani et al. As noted by Jani: 1) when Ir-192 seed sources with a total activity of ≤600 mCi were employed in coronary brachytherapy, the exposure rates around typical cath lab rooms were well within regulatory levels; and 2) with a prudent radiation safety program in place, in over 500 intracoronary brachytherapy procedures with Ir-192 (at SCRIPPS Clinic), there has not been any significant additional radiation exposure to the catheterization laboratory personnel.

The incremental radiation to the patient during one intravascular brachytherapy session is approximately equal to one additional angioplasty procedure.

**Conclusion.** The diagnostic or therapeutic use of any form of radiation is associated with a certain risk of adverse events. However, in the patient population with severe in-stent restenosis, these risks have to be weighed against the risks and costs of repeated percutaneous interventions and/or bypass surgery. Based on the available efficacy and safety data, intravascular brachytherapy using the CHECKMATE gamma radiation system seems safe for routine use in these patients by an appropriately trained, multidisciplinary team that encompasses both the necessary specialized knowledge relating to interventional cardiology as well as radiation therapy in institutions licensed to handle the relevant radioactive sources. A Food and Drug Administration (FDA) Advisory Panel unanimously recommended approval of this system on June 19, 2000 and the FDA approved the system for sale on November 3, 2000.

**REFERENCES**

6. Kuntz RE. Personal communication.