Intracoronary Radiation Therapy Improves the Clinical and Angiographic Outcomes of Diffuse In-Stent Restenotic Lesions

Results of the Washington Radiation for In-Stent Restenosis Trial for Long Lesions (Long WRIST) Studies

Ron Waksman, MD; Edouard Cheneau, MD; Andrew E. Ajani, MD; R. Larry White, MD; Ellen Pinnow, MS; Rebecca Torguson, BS; Regina Deible, RN; Lowell F. Satler, MD; Augusto D. Pichard, MD; Kenneth M. Kent, MD; Paul S. Teirstein, MD; Joseph Lindsay, MD

Background—The Washington Radiation for In-Stent Restenosis Trial for long lesions (Long WRIST) was designed to determine the safety and efficacy of vascular brachytherapy for the treatment of diffuse in-stent restenosis.

Methods and Results—A total of 120 patients with diffuse in-stent restenosis in native coronary arteries (lesion length, 36 to 80 mm) were randomized for either radiation with 192 Ir with 15 Gy at 2 mm from the source axis or placebo. After enrollment, 120 additional patients with the same inclusion criteria were treated with 192 Ir with 18 Gy and included in the Long WRIST High Dose registry. Antiplatelet therapy was initially prescribed for 1 month and was extended to 6 months in the last 60 patients of the Long WRIST High Dose registry. At 6 months, the binary angiographic restenosis rate was 73%, 45%, and 38% in the placebo, 15 Gy, and 18 Gy radiated groups, respectively \( P<0.05 \). At 1 year, the primary clinical end point of major cardiac events was 63% in the placebo group and 42% in the radiated group with 15 Gy \( P<0.05 \). The major cardiac event rate was further reduced with 18 Gy \( P<0.05 \) versus 15 Gy). Late thrombosis was 12%, 15%, and 9% in the placebo group, 15 Gy group with 1 month of antiplatelet therapy, and 18 Gy group with 6 months of antiplatelet therapy, respectively.

Conclusions—Vascular brachytherapy with 192 Ir is safe and reduces the rate of recurrent restenosis in diffuse in-stent restenosis. The efficacy of vascular brachytherapy on angiographic and clinical outcomes is enhanced with a radiation dose of 18 Gy and prolonged antiplatelet therapy. (Circulation. 2003;107:1744-1749.)

Key Words: brachytherapy ■ restenosis ■ lesion ■ radiation
and successful percutaneous coronary intervention of the ISR lesion with balloon angioplasty, atheroablation (laser or rotational atherectomy), or restenting. Major exclusion criteria included recent (<72 hours) acute myocardial infarction, ejection fraction <20%, angiographic thrombus, and/or allergy to APT. Patients were randomly assigned to -radiation with 192 Ir with 15 Gy at 2 mm from the center of the source (n = 60) or placebo therapy (n = 60). APT (clopidogrel or ticlopidine) was prescribed for 1 month after intervention in addition to aspirin (250 mg/d).

**Long WRIST High Dose**

Long WRIST High Dose was designed as a prospective registry of 120 consecutive patients who presented with symptoms of angina with long and diffuse ISR in a native coronary artery. Inclusion and exclusion criteria were similar to the Long WRIST study. Patients were treated with 192 Ir radiation with 18 Gy at 2 mm from the center of the source. The duration of APT was extended at the midpoint of the study from 1 month to 6 months; this was driven by the recognition and the need for prevention of late thrombosis seen in other radiation trials for ISR. Patients were analyzed according to the duration of APT (1 month, n = 60; 6 months, n = 60).

**Radiation Details and Dosimetry**

Percutaneous coronary intervention was performed using conventional strategies. After the intervention, a closed-end-lumen, noncentered catheter (Cordis checkmate or Medtronic AVE) with a side guide 0.014-inch wire was introduced into the artery. A ribbon with different trains of 14, 17, 19, or 23 placebo or 192 Ir seeds (Best Medical International; lengths of 55 to 91 mm) was positioned by hand to cover the treated site. All seeds were equal in length (3 mm separated with a 1 mm space) with a mean specific activity of 25.3 ± 3.5 mCi.

The prescribed radiation dose for Long WRIST was 15 Gy at 2 mm radial distance in vessels ≤4 mm in diameter (to 2.4 mm in vessels 4 to 5 mm) or dummy seeds (placebo). The prescribed radiation dose for Long WRIST High Dose was 18 Gy to a 2 mm radial distance in vessels ≤4 mm in diameter.

**End Points and Follow-Up**

The primary clinical end points were late thrombosis and the composite major cardiac events (MACE) of death, myocardial infarction, and target lesion revascularization rate at 12 months. Secondary angiographic end points were late total occlusion (LTO), binary restenosis, and late loss at 6 months angiographic follow-up. Late thrombosis was defined as angiographic evidence of thrombus or the presence of myocardial infarction related to the treated vessel 30 days after the radiation. An independent committee adjudicated all events. LTO was defined angiographically as a minimum lumen diameter (MLD) of 0 mm.

**Angiographic Analysis**

Quantitative coronary angiographic analysis was performed at the initial procedure and at follow-up (4 to 8 months after treatment) independently by a core angiographic laboratory blinded to the treatment assignment using the CMS-GFT system (Medis). The mean reference vessel diameter was obtained from averaging 5-mm-

### TABLE 1. Baseline Clinical and Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Long WRIST Placebo (n=60)</th>
<th>Long WRIST Radiation (n=60)</th>
<th>Long WRIST High Dose 1 Month of APT Placebo (n=60)</th>
<th>Long WRIST High Dose 1 Month of APT Radiation (n=60)</th>
<th>Long WRIST High Dose 6 Months of APT Placebo (n=60)</th>
<th>Long WRIST High Dose 6 Months of APT Radiation (n=60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±10</td>
<td>63±10</td>
<td>60±9</td>
<td>57±11</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males, %</td>
<td>62</td>
<td>67</td>
<td>72</td>
<td>50</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers, %</td>
<td>67</td>
<td>63</td>
<td>57</td>
<td>67</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>68</td>
<td>68</td>
<td>75</td>
<td>80</td>
<td>0.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>37</td>
<td>42</td>
<td>42</td>
<td>48</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>87</td>
<td>85</td>
<td>87</td>
<td>93</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>58</td>
<td>60</td>
<td>52</td>
<td>45</td>
<td>0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous CABG, %</td>
<td>39</td>
<td>37</td>
<td>29</td>
<td>33</td>
<td>0.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>48</td>
<td>45</td>
<td>36</td>
<td>40</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>50±11</td>
<td>50±12</td>
<td>51±10</td>
<td>53±11</td>
<td>0.69</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD or percentage. MI indicates myocardial infarction; CABG, coronary artery bypass grafting; and LV, left ventricular.

### TABLE 2. Procedural Summary

<table>
<thead>
<tr>
<th></th>
<th>Long WRIST Placebo (n=60)</th>
<th>Long WRIST Radiation (n=60)</th>
<th>Long WRIST High Dose 1 Month of APT Placebo (n=60)</th>
<th>Long WRIST High Dose 1 Month of APT Radiation (n=60)</th>
<th>Long WRIST High Dose 6 Months of APT Placebo (n=60)</th>
<th>Long WRIST High Dose 6 Months of APT Radiation (n=60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Main, %</td>
<td>3.3</td>
<td>5</td>
<td>1.7</td>
<td>0.0</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD, %</td>
<td>23</td>
<td>22</td>
<td>22</td>
<td>20</td>
<td>0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCX, %</td>
<td>33</td>
<td>22</td>
<td>22</td>
<td>13</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA, %</td>
<td>40</td>
<td>51</td>
<td>53.3</td>
<td>67</td>
<td>0.048</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotational atherectomy, %</td>
<td>67</td>
<td>68</td>
<td>58</td>
<td>50</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excimer laser, %</td>
<td>20</td>
<td>18</td>
<td>23</td>
<td>13</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional stenting, %</td>
<td>59</td>
<td>72</td>
<td>60</td>
<td>47</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon angioplasty, %</td>
<td>100</td>
<td>98</td>
<td>98</td>
<td>98</td>
<td>0.71</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LAD indicates left descending artery; LCX, left circumflex artery; and RCA, right coronary artery.
long angiographically normal segments proximal and distal to the lesion. MLD was used to calculate percent diameter stenosis as follows: \[\frac{\text{lesion}}{\text{reference vessel diameter}}\times 100\]. Angiographic binary restenosis at follow-up was defined as \(\geq 50\%\) diameter narrowing. Total analyzed segment included 5 mm proximal and 5 mm distal to the ribbons. A luminal diameter of 0 mm was imputed in the presence of a total occlusion at baseline or at follow-up. Acute gain (in millimeters) was defined as the change in MLD from baseline to the final procedural angiogram. Late loss (in millimeters) was defined as the change in the MLD from the final to the follow-up angiogram.

### Statistics

The target sample size of the Long WRIST study was determined (80% power and 95% confidence) to demonstrate a 50% reduction in the primary clinical end point of composite cardiac events (expecting primary end point rate of 50% in the placebo group). Groups were analyzed by intention to treat. Continuous variables were expressed as mean±SD and categorical data as percentages. Student’s \(t\) test was used to compare continuous variables; \(\chi^2\) statistics or Fisher’s exact test were used to compare categorical values.

### Results

#### Study Population

From January 1998 to July 1999, 240 patients were enrolled in the Long WRIST trials. A total of 120 patients with recurrent ISR were enrolled in the Long WRIST study and another 120 patients were enrolled in Long WRIST High Dose. Clinical characteristics are presented in Table 1 and were identical in the placebo arm and the treatment arm of the Long WRIST study. Patients enrolled in the Long WRIST High Dose registry were identical to those randomized in the Long WRIST study.

#### Procedure and Radiation

Radiation was successfully delivered in all patients in the radiated arms. Dwell time was 19.3±3.6 minutes with 15 Gy and 25.2±3.4 minutes with 18 Gy. Sources of 14, 17, 19, and 23 seeds were used in 11%, 30%, 28%, and 31% of the cases, respectively. Procedural details are shown in Table 2. No difference in pre- and postprocedural angiographic characteristics was observed between the placebo arm and the radiated arms of the Long WRIST study. Lesions were longer with a smaller MLD in Long WRIST High Dose than in the Long WRIST study.

#### Angiographic Follow-Up

At 6 months, angiograms were available in 47, 47, 51, and 49 patients of the Long WRIST placebo, Long WRIST radiated,
Long WRIST High Dose 1 month APT, and Long WRIST High Dose 6 months APT groups (Table 3). The MLD was larger in radiated arteries with 15 Gy than in the placebo group. Late loss was slightly reduced with radiation with 15 Gy (0.65±0.81 mm versus 0.85±0.54 mm in the placebo arm; \(P=0.16\)). Further reduction of late loss was observed with a higher radiation dose; late loss was 0.46±0.76 mm with 18 Gy (\(P<0.05\) versus 15 Gy).

The binary restenosis rate was lower in the radiated arm of Long WRIST study than in the placebo arm in all angiographic segments analyzed (Figure 1). Compared with placebo, the binary restenosis rate in the total analyzed segment was reduced by 38% with 15 Gy and 48% with 18 Gy. The binary restenosis rate was not influenced by the duration of APT (38% and 39% with 1 and 6 months APT, respectively).

**Clinical Outcomes**

Clinical outcomes are presented Table 4. In-hospital outcome was similar between all the groups. No in-hospital death was reported.

Clinical follow-up was available in all patients at 12 months (Figure 2). Sixteen patients of the Long WRIST placebo group presenting with a major cardiac event during the follow-up were crossed over and treated with \(^{192}\)Ir.

One patient in the placebo group, 4 in the radiated group of Long WRIST, and 1 in Long WRIST High Dose died during the 12-month follow-up (\(P=\text{NS}\)). Compared with the placebo group, radiated patients in the Long WRIST study had lower target lesion revascularization rate (39% versus 61.7%, \(P=0.011\)) and cardiac events at 12 months (42.4% versus 63.3%; \(P=0.017\)). Additional reduction of target lesion

### Table 4. Clinical Outcomes

<table>
<thead>
<tr>
<th>In hospital</th>
<th>Long WRIST Placebo (n=60)</th>
<th>Radiation (n=60)</th>
<th>Long WRIST High Dose 1 Month of APT (n=60)</th>
<th>Long WRIST High Dose 6 Months of APT (n=60)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CK-MB &gt;3× normal, %</td>
<td>16.7</td>
<td>11.7</td>
<td>18.3</td>
<td>10.3</td>
<td>0.54</td>
</tr>
<tr>
<td>Q-wave MI, %</td>
<td>0</td>
<td>1.7</td>
<td>0</td>
<td>0</td>
<td>0.39</td>
</tr>
<tr>
<td>Non-Q-wave MI, %</td>
<td>0</td>
<td>3.3</td>
<td>0</td>
<td>1.7</td>
<td>0.29</td>
</tr>
<tr>
<td>12-Month follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths, %</td>
<td>1.7</td>
<td>6.8</td>
<td>0</td>
<td>2.2</td>
<td>0.13</td>
</tr>
<tr>
<td>Q-wave MI, %</td>
<td>0</td>
<td>6.8</td>
<td>0</td>
<td>0</td>
<td>0.028</td>
</tr>
<tr>
<td>Non-Q-wave MI, %</td>
<td>18.3</td>
<td>16.9</td>
<td>17.9</td>
<td>17.4</td>
<td>0.99</td>
</tr>
<tr>
<td>TLR, %</td>
<td>61.7</td>
<td>39.0*</td>
<td>19.6</td>
<td>19.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TLR-MACE, %</td>
<td>63.3</td>
<td>42.4*</td>
<td>21.7†</td>
<td>19.6†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late thrombosis, %</td>
<td>11.7</td>
<td>15.3</td>
<td>8.9</td>
<td>8.7</td>
<td>0.67</td>
</tr>
</tbody>
</table>

CK indicates creatine kinase; MI, myocardial infarction; TLR, target lesion revascularization; and MACE, major adverse cardiac event.

\(P<0.05\): *Long WRIST vs placebo, †Long WRIST High Dose 1 month APT vs Long WRIST.
revascularization and cardiac events was observed with a higher radiation dose (target lesion revascularization rate and MACE were 19.6% and 21.7% in the Long WRIST 1 month APT group; \( P = 0.10 \) and \( P = 0.048 \), respectively, versus Long WRIST). Target lesion revascularization rate and MACE were 19.6% in the Long WRIST 6-month APT group.

**Thrombotic Events**

LTO occurred in 7 patients (11.7%) in the placebo group and in 18 patients (10%) in the pooled radiated groups (\( P = 0.90 \)). LTO occurred in 9 patients in the Long WRIST radiated group (\( P = 0.59 \) versus the placebo group) and 5 in the Long WRIST High Dose with 1 month APT. In the Long WRIST high dose with 6 months APT, LTO occurred in only 4 patients; one of them presented with LTO after prematurely discontinuing APT. Five patients presented with angiographic LTO without a clinical event.

**Discussion**

The Long WRIST series of studies shows that VBT is safe and effective in reducing the rate of recurrence of long and diffuse ISR. In the randomized, controlled study, VBT reduced the rate of angiographic restenosis by 38% and the rate of major cardiac events compared with placebo by 33%. Increasing the dose from 15 Gy to 18 Gy provided further reduction of restenosis, and when APT was extended to 6 months follow-up, the risk for late thrombosis with 18 Gy was comparable to patients treated with placebo.

**Dose and Efficacy**

VBT has demonstrated efficacy in reducing ISR.\(^8\)–\(^10\) However, in the pivotal clinical trials evaluating this technology (Scripps Coronary Radiation to Inhibit Proliferation Post Stenting [SCRIPPS]),\(^6\) Washington Radiation for In-Stent restenosis Trial [WRIST],\(^7\) Localized Intracoronary Gamma-Radiation Therapy to Inhibit the Recurrence of Restenosis after Stenting [GAMMA I],\(^8\) and Intimal Hyperplasia Inhibition with Beta In-stent Trial [INHIBIT])\(^9\) trials), the inclusion criteria were limited to lesion lengths of up to 47 mm; in the Sr90 Treatment of Angiographic Restenosis (START)\(^10\) trials, lesion length was \( \leq 20 \) mm. The Long WRIST studies focused on patients with diffuse ISR with lesions between 36 and 80 mm in length. In these studies, the findings of high recurrence rate in the placebo group was expected, but the cardiac event rate of 42% in the irradiated vessels with 15 Gy was higher than previously reported in the VBT studies with shorter lesions using the same source \(^{192}\)Ir in native and saphenous vein graft ISR lesions with a dose of 14 to 15 Gy.\(^6\)–\(^8\),\(^11\) These findings led the investigators to initiate the Long WRIST High Dose registries with dose escalation of 18 Gy.

The Long WRIST High Dose registry examined the hypothesis that a higher dose of 18 Gy can improve the efficacy of radiation without increasing vessel toxicity for diffuse ISR. Previously, we reported that an intravascular ultrasound analysis on a selective group of patients from these studies showed that VBT with 15 Gy might be less effective in long lesions because of the greater variability and longer source-to-target distances in these lesions.\(^12\) In addition, intravascular ultrasound analysis of the Long WRIST trials showed further reduction of intimal hyperplasia with 18 Gy compared with 15 Gy.\(^13\)

The current study demonstrated that a higher dose resulted in additional reduction of late loss and, consequently, led to larger vessel diameter at 6 months. VBT with 18 Gy reduced the binary restenosis rate by 48% compared with control and by 22% compared with 15 Gy; this reduction was translated to reduction for the need for revascularization at 12 months.

The current recommended dose for the checkmate system is 14 Gy at 2 mm from the source. This dose was approved for use based on the data from the GAMMA 1 and 2 and the WRIST studies.\(^14\) The present study demonstrates that a dose of 18 Gy at 2 mm is more effective in reducing target vessel revascularization and is associated with prolonged dwell time but without any adverse angiographic and clinical events. The proposed higher dose may further reduce the recurrences observed beyond 6 months that were reported in both the SCRIPPS\(^15\) and WRIST\(^16\) studies.
Debulking strategies in the present study did not provide further optimization of the outcome when compared with balloon angioplasty in both groups with and without VBT and potentially may be associated with higher rates of non-Q-wave myocardial infarction, as described previously in other VBT studies for ISR.17

Thus, the main recommendation for outcome optimization is to increase the dose of the $^{198}$Ir for diffuse lesions to 18 Gy.

Safety and Late Thrombosis

Irradiation of long segments in coronary arteries up to 91 mm was not associated with procedural and late angiographic complications. There was no excess of spasm, aneurysm, or fibrosis. In the study, the radiation margin ranged between 5 to 10 mm from the injured segment.

The rate of LTO in Long WRIST with 1 month of APT was 15.3% in the radiated arteries compared with 11.7% in the placebo. These high rates of late thrombosis were similar to the previously reported rate of LTO in the radiation studies with 1 month of APT.18 Higher doses with 18 Gy also did not increase the rate for thrombotic events. However, prolonged APT to 6 months prescribed to the last 60 patients from the Long WRIST High Dose registry was associated with significant reduction of the late thrombosis rate in the 18 Gy group. With prolonged APT, the thrombotic rate was similar in radiated (18 Gy) and nonradiated arteries during the 12 months of follow-up.

The Long WRIST studies demonstrated that the long-term outcome could be optimized with an increase in the dose to 18 Gy and prolonged APT. With the combination of these 2 changes, increase of the dose and prolonged APT, 78% of the patients were free of cardiac events at 12 months compared with 37% in the placebo group. With the recent report from WRIST 12, we recommend a minimum of 12 months of APT for any patients treated with VBT.19 Further improvements in the outcome may also be accomplished by carefully adding adequate margins (minimum of 10 mm from the injured segment). Yet with nearly 20% MACE with 18 Gy, we should reconsider the stenting of long lesions and continue to explore whether higher doses will continue to reduce the recurrent rate. These strategies are currently being tested with a dose of 21 Gy in the in the WRIST 21 study.

Limitations

This study was limited to 12 months of follow-up and the impact of late thrombosis might have been underestimated. The rate of angiographic follow-up is low and could not represent the true binary restenosis for the entire cohort.

Conclusions

The Long WRIST studies show that long ISR lesions are safely treated with VBT. $\gamma$-Radiation with 15 Gy reduces the rate of restenosis and the subsequent need for revascularization in such lesions. Angiographic and clinical outcomes are further improved with a radiation dose of 18 Gy, and the risk for thrombotic events is similar to placebo treatment when APT is continued for at least 6 months.

References

Intracoronary Radiation Therapy Improves the Clinical and Angiographic Outcomes of Diffuse In-Stent Restenotic Lesions: Results of the Washington Radiation for In-Stent Restenosis Trial for Long Lesions (Long WRIST) Studies
Ron Waksman, Edouard Cheneau, Andrew E. Ajani, R. Larry White, Ellen Pinnow, Rebecca Torguson, Regina Deible, Lowell F. Satler, Augusto D. Pichard, Kenneth M. Kent, Paul S. Teirstein and Joseph Lindsay

_Circulation_. 2003;107:1744-1749; originally published online March 24, 2003;
doi: 10.1161/01.CIR.0000060497.91775.6D
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/13/1744

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/