Coronary Brachytherapy: Something New, Something Old
64th Annual AAPM Meeting

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July 12th, 2022

Other key Yale team members:
- Steven Pfau, MD
- Dae Y. Han, Ph.D
- James E. Hansen, MD
- Glen Henry, MD

Coronary Brachytherapy:
nothing to declare.
Outline

• Introduction
  – Coronary Artery Disease, Epidemiology and Cath Lab management
• In-stent restenosis – treatment using brachytherapy
• Coronary Brachytherapy Workflow and dosimetry
• Intravascular Brachytherapy (IVBT) – Pivotal Trials
• Adverse effects of coronary brachytherapy
• Evidence for brachytherapy in the DES era
• Challenging clinical scenarios for coronary brachytherapy

Coronary Artery Disease

• Atherosclerotic vascular disease remains the number one cause of death globally
  – 32% of all global deaths.
  • 8.9 million deaths from CAD and 6.2 million from CVA in 2019.

• Cardiac deaths, USA - 659,000/yr
  – Nearly a quarter of all deaths
  – Cancer a close second

• >90 million in US with CAD

• Each year 805,000 US adults experience a MI/yr
A Brief Introduction to Cardiac Anatomy

Coronary Artery Disease

- Treatments include control of risk factors, drug therapy, coronary bypass graft surgery (CABG), and percutaneous coronary interventions (PCI) including balloon dilation and stenting.

- Restenosis rates after PCI
  - 30-40% after angioplasty
  - 20-30% after “bare-metal” stenting
  - 3-7% after drug-eluting stents (DES)
  - 20-80% of patients treated for in-stent stenosis, have restenosis.
Procedure Details

- Conscious sedation
- Local anesthesia
- Arterial access via radial, brachial or femoral artery
- 6F (2mm) catheter used most commonly
- Catheters placed in all 4 chambers to record pressure and flow (cardiac output)
- Catheter positioned for selective coronary angiography
Left Coronary Artery
Right Coronary Artery
Coronary Angioplasty

- Nonsurgical dilation of obstructive coronary plaque
- Commonly used as an aid to management of angina
- Preferred treatment of acute myocardial infarction
- Most angioplasties include the placement of an intracoronary stent
First PTCA, Gruentzig, Zurich Sept 1977, with 10 year (and later 23 year) follow-up

IV heparin, dextran, and aspirin for 3 days

Yale Interventional Cardiology
Size of an expanded coronary stent in relation to a dime


Yale Interventional Cardiology

Neo-Intimal Hyperplasia – “In-stent” Restenosis
Clinical factors: High risk subgroups for ISR

- Diabetes
- Long lesions
- Narrow vessels
- Vein grafts
- Renal failure
- Prior ISR

In-stent Restenosis

- Tissue grows through and around the stent over time. This causes a partial blockage of the artery and abnormal blood flow. The inset image shows a cross-section of the tissue growth around the stent.

- Stents coated with medicine (drug-eluting stents, DES) reduce the growth of scar tissue around the stent.

- Radiation, can also help prevent tissue growth within a stent.
In-stent Restenosis -- Scope of the Problem

965,000 PCIs in USA Annually

80% use stents, mostly DES

10% require retreatment for ISR
two-thirds of ISR cases occur post-DES

Coronary Brachytherapy - Workflow

1. Repeat angioplasty and other PCI performed to enlarge the lumen

2. Intravascular ultrasound or OCT performed to assist with dose calculation/selection

3. Radioactive source train placed into the target coronary within catheter, position verified by fluoroscopy
Novoste Beta-Cath – Sr90/Y90 source system

3.5F Monorail Delivery Catheter;
30, 40 and 60mm Source Trains

Brachytherapy Team (Mandated by FDA Regulation)

- Interventional cardiologist
- Radiation oncologist
- Medical physicist
- Radiation safety officer
Coronary Brachytherapy Prescription/Written Directive

1. Target Vessel Identification
2. Injury Length (via intracoronary imaging, fiducial marker wire, and reference to stent and angioplasty balloon lengths)
3. Target Length (adding at least 5-10 mm margin)
4. Source train length choice
5. Prescribed dose based on mean luminal diameter

FDA approval of Beta-Cath START trial resulted in a simple binary prescription: 
<3.4 mm 23 Gy at 2 mm depth; ≥ 3.4 mm 18.4 Gy at 2 mm depth

6. Dwell time from look-up table

Recurrent ISR – Interventional Approach

- Intracoronary Imaging
  - Optical Coherence Tomography (OCT)
  - Intravascular Ultrasound (IVUS)
- Details of the Target:
  - Optimal stent expansion?
  - Diameter
  - Length
Recurrent ISR – Interventional Approach

- Optimize Lumen
- Add as few stents as possible
- Brachytherapy

Angiographic view of BetaCath source train in RCA
Method of Intravascular Ultrasound (IVUS) Interrogation

Nissen, S. E. et al. JAMA 2003;290:2292-2300.

Yale Interventional Cardiology

Restenosis

Fully expanded stent
Rationale for Brachytherapy – What is the data?

- In-stent restenosis is a non-malignant proliferative, inflammatory response
- Radiation is effective to prevent keloids, pterygium, heterotopic bone formation
- Radiation proved effective in animal models of arterial injury and intimal proliferation
- Multiple Phase III trials with positive results for coronary brachytherapy to treat ISR associated with bare metal stents leading to FDA device approvals

Isotopes Used in Intravascular Brachytherapy

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Emission</th>
<th>Half-life</th>
<th>Energy in MeV</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Avg</td>
<td>Max</td>
</tr>
<tr>
<td>192Ir</td>
<td>Gamma</td>
<td>74 days</td>
<td>0.37</td>
</tr>
<tr>
<td>32P</td>
<td>Beta</td>
<td>14 days</td>
<td>0.69</td>
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<tr>
<td>90Sr</td>
<td>Beta</td>
<td>28 years</td>
<td>0.20</td>
</tr>
<tr>
<td>90Y</td>
<td>Beta</td>
<td>64 hours</td>
<td>0.90</td>
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</table>
Beta and Gamma Radiotherapy

**Beta:**
- Negligible rad safety concerns, less shielding
- Poorer depth dose and target dose homogeneity
- Shorter delivery time (2-10 min)
- Concerns about efficacy in larger vessels

**Gamma:**
- Higher energy = more patient/staff exposure, need for more shielding
- Better depth dose
- Longer delivery time (15-30 min)
- Broader spectrum of vessel sizes

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Depth-dose for Beta and Gamma sources

- **Ir-192**
- **P-32**
Dosimetry of intravascular brachytherapy linear source arrays

- Dose gradient at radial depth is steep such that variation in dose is seen with variable lumen diameter
- Off-centering of sources within lumen and produce large variation in dose delivery to vessel wall
- Vessel curvature is minor factor assuming source centering

Radiation Dose perturbations from stents and calcifications

Effect of stent on radiation dosimetry in an in-stent restenosis model

For beta-sources:
- 20% dose reduction immediately behind the stent struts
- 8-11% dose increase in front of stent struts
- 5% dose increase between struts
- *** at depth beyond stent, dose matches no-stent due to electron scatter

For gamma-sources
- dose perturbations depend on photon energy, but for Ir-192 – common isotope used for HDR brachytherapy, there are minimal dose perturbations.

Calcium deposits in wall of artery or multiple stent-in-stent scenarios are not well studied, but probably associated with significant shadowing effects for beta-emitters
Intravascular Brachytherapy (IVBT) Trials – pre DES

- Intracoronary radiation aims at reducing the risk of in-stent restenosis
- IVBT trials showed advantages on in-stent restenosis

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Source</th>
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<tbody>
<tr>
<td>SCRIPPS I</td>
<td>Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting Ir-192</td>
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<tr>
<td>WRIST</td>
<td>The Washington Radiation In-Stent Trial Ir-192</td>
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<tr>
<td>LONG WRIST</td>
<td>Ir-192</td>
</tr>
<tr>
<td>SVG WRIST</td>
<td>Ir-192</td>
</tr>
<tr>
<td>BETA WRIST</td>
<td>Sr-90/T-90</td>
</tr>
<tr>
<td>BERT</td>
<td>Beta Energy Restenosis Trial Sr-90</td>
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<tr>
<td>PARIS</td>
<td>Peripheral Artery Radiation Investigative Study Ir-192</td>
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<td>Beta-Cath &amp; START</td>
<td>Beta-Cath Trials Sr-90/T-90</td>
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<tr>
<td>ARREST</td>
<td>Angiorad Radiation for Restenosis Unstented native Vessel Ir-192</td>
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<tr>
<td>PREVENT</td>
<td>periferation Reduction with Vascular Energy Trial P-32</td>
</tr>
<tr>
<td>Gamma-I</td>
<td>Ir-192</td>
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</table>

List of Intravascular Brachytherapy Trials

GAMMA-1 -- Pre-DES pivotal trial of Ir-192 brachy for ISR

- Multicenter, randomized, double-blinded
- Ir\(^{192}\) source wires, IVUS guided dose prescription
  - Manually feed source wires used 3 mm sources with 1 mm spacers for 23, 39, and 55 mm effective lengths.
  - Target was the internal elastic membrane (media/adventitia interface) prescribed maximum of 30 Gy with minimum of 8 Gy if possible.
- 252 patients
- angiographic binary restenosis at 6 months
- At least 8 wks anti-platelet therapy post-procedure

### GAMMA-1

<table>
<thead>
<tr>
<th></th>
<th>IRT (%)</th>
<th>Placebo (%)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>6 mo restenosis*</td>
<td>32.4</td>
<td>55.8</td>
<td>0.01</td>
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<tr>
<td>In-stent</td>
<td>21.6</td>
<td>50.5</td>
<td>0.005</td>
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<tr>
<td>TLR at 9 mo</td>
<td>24.4</td>
<td>42.1</td>
<td>&lt;0.01</td>
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<tr>
<td>MACE 9 mo</td>
<td>28.2</td>
<td>43.8</td>
<td>0.02</td>
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<tr>
<td>Late thrombosis</td>
<td>5.3</td>
<td>0.8</td>
<td>0.07</td>
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</table>

*Leon NEJM, 2001*

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### Novoste Beta-Cath – Sr90/Y90 source system

- 3.5F Monorail Delivery Catheter
- 30, 40 and 60mm Source Trains
**START – pivotal trial of BetaCath system for ISR, pre-DES era**

- Randomized, double-blinded, multicenter
- 476 patients with in-stent restenosis
- 8 month angiographic follow-up
- 18.4 or 23 Gy at 2mm depth from Sr$^{90}$/Y$^{90}$ source based on mean luminal diameter threshold of 3.4 mm
- Hydraulic delivery system.

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**START -- Results**

<table>
<thead>
<tr>
<th></th>
<th>IRT (%)</th>
<th>Placebo (%)</th>
<th>P value</th>
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<tbody>
<tr>
<td>8 mo restenosis</td>
<td>24.4</td>
<td>45.9</td>
<td>&lt;0.001</td>
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<tr>
<td>In-stent</td>
<td>14.2</td>
<td>41.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TLR at 8 mo**</td>
<td>17</td>
<td>26.8</td>
<td>0.015</td>
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<tr>
<td>MACE at 8 mo</td>
<td>19.1</td>
<td>28.7</td>
<td>0.024</td>
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</table>

*Popma, Circulation 2002*
Slide 45

Target Vessel Revascularization

- START: Placebo 24.1 vs. Radiation 16
- GAMMA 1: Placebo 47.9 vs. Radiation 33.6
- INHIBIT: Placebo 31 vs. Radiation 20

34% ↓, 30% ↓, 35% ↓

Slide 46

MACE

- START: Placebo 25.9 vs. Radiation 18
- GAMMA 1: Placebo 43.8 vs. Radiation 28
- INHIBIT: Placebo 33 vs. Radiation 22

31% ↓, 36% ↓, 33% ↓
## FDA Approved Systems: Clinical Indications and Usage

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Novoste BetaCath&lt;sup&gt;TM&lt;/sup&gt;</th>
<th>Cordis Checkmate&lt;sup&gt;TM&lt;/sup&gt;</th>
<th>Guidant Galileo&lt;sup&gt;TM&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion Length</td>
<td>“Treatable with 20 mm balloon”</td>
<td>Up to 45 mm</td>
<td>Up to 47 mm</td>
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<tr>
<td>Vessel diameter</td>
<td>2.7 – 4.0 mm</td>
<td>2.75 – 4.0 mm</td>
<td>2.4 – 3.7 mm</td>
</tr>
<tr>
<td>Source</td>
<td>Beta (90&lt;sup&gt;Sr&lt;/sup&gt;/&lt;sup&gt;Y&lt;/sup&gt;)</td>
<td>Gamma (192&lt;sup&gt;Ir&lt;/sup&gt;)</td>
<td>Beta (32&lt;sup&gt;P&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Cannot take antiplatelet or anticoagulant</td>
<td>Cannot take antiplatelet or anticoagulant</td>
<td>Cannot take antiplatelet or anticoagulant</td>
</tr>
</tbody>
</table>

**FDA Approved Brachytherapy Systems**

**Gamma: Cordis CheckMate<sup>TM</sup>**
FDA Approved Brachytherapy Systems

Guidant: Galileo™ System

Centering Catheter 27mm / 2.5-3.5mm

Nitinol Wire

32P 27mm .018in

Source Delivery Unit

3-lumen, closed end

Transfer device using hydraulic delivery of the source train

Delivery Catheter 3-lumen, closed end

FDA Approved Brachytherapy Systems

Beta: Novoste BetaCath™
Radiotherapy-Adverse Effects

• “Edge effects”
• Late thrombotic occlusion
• Long-term effects

“Edge Effect”

• Occurrence: 3-15%
• Related to “Geographic Miss” (injury + low dose radiation)
• Mechanism: Paradoxical neointimal hyperproliferation and constrictive remodeling
• Minimized by use of wide (3-5 mm) radiation margin

Post-Stent  Brachytherapy  6 Months
Geographic Miss (GM) and Likelihood of Edge Restenosis

**BRIE Trial**

- Proximal edge
- Distal edge
- Edges

Geographic miss is the primary cause of edge restenosis.

Radiotherapy-Specific Effects

- “Edge effects”
- Late thrombotic occlusion
- Long-term effects
Late (>30 d) Thrombotic Events
After Vascular Brachytherapy

- Occurrence: 5 - 10% in early trials
- Primarily (but not entirely) in newly stented arteries!!!
- Attributed to delayed reendothelialization
- Minimized by prolonged antiplatelet (thienopyridines) therapy

Late Clinical Thrombosis in Radiotherapy Trials for In-Stent Restenosis
With Prolonged Antiplatelet (Thienopyridine) Therapy and
Provisional Stenting

<table>
<thead>
<tr>
<th>Trial</th>
<th>Months of Ticlid/Plavix</th>
<th>% New Stents</th>
<th>Months of F/U</th>
<th>Late Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCRIPPS III</td>
<td>6</td>
<td>26%</td>
<td>6</td>
<td>0%</td>
</tr>
<tr>
<td>WRIST Plus</td>
<td>6</td>
<td>29%</td>
<td>6</td>
<td>0%</td>
</tr>
<tr>
<td>START</td>
<td>3</td>
<td>21%</td>
<td>9</td>
<td>0%</td>
</tr>
<tr>
<td>INHIBIT</td>
<td>6</td>
<td>28%</td>
<td>9</td>
<td>1%</td>
</tr>
</tbody>
</table>
Radiotherapy-Specific Effects

• “Edge effects”
• Late thrombotic occlusion
• Long-term effects (exceeding rare or not-reported)
  – Aneurysms
  – Perforations
  – Secondary Malignancy

Coronary Brachytherapy

• Brachytherapy is an effective treatment for in-stent restenosis
• Mid-term (3-5 yr) safety established
• Efficacy maintained in highest risk subgroups
**Drug Eluting Stents v IVBT: TAXUS V ISR Trial**

396 patients > 18 years with stable or unstable angina or inducible ischemia undergoing percutaneous coronary intervention (PCI) of a single bare-metal in-stent restenosis (ISR) lesion in a native coronary artery. Randomized. 34% female, median age 63 years, mean follow-up 9 months

Angiography (Baseline)

- VBT using a beta-source radiation
  - n=201
- PCI with paclitaxel-eluting stents
  - n=195

Repeat Angiography (9 months)
- 170 in VBT group and 172 in Paclitaxel group

Primary Endpoint: Ischemia-driven target vessel revascularization at 9 months

Presented at ACC 2006

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**TAXUS V ISR Trial: Primary Endpoint**

Ischemic Target Vessel Revascularization at 9 months (%)

- p=0.046

- The primary endpoint of ischemic target vessel revascularization was higher in the VBT group compared with the paclitaxel group at 9 months (17.5% vs 10.5%; p=0.046)
What are the Rx options for DES-ISR?

Balloon Angioplasty
Repeat stenting – bare metal stent another DES
Rotational atherectomy
Laser atherectomy
Drug-coated balloons
Bypass surgery
Coronary Brachytherapy**

** but IVBT not well studied after DES ISR

What are the results of IVBT post-DES ISR?

Limited numbers of retrospective trials,

but enough to justify the use of coronary brachytherapy in this off-label application for high-risk patients having repeated trips to the coronary cath lab for PCI
MACE at one year improved in brachy patients (13.2% and 28.2%; P=0.01).

A propensity score matched cohort of 182 patients showed MACE at one year of 13.2% v 30.8%, P<0.01 favoring brachytherapy.
Challenging Clinical Scenarios: reRx and long lesions

- Retreatment with brachytherapy – appears safe if at least 9 months between treatments
- Long lesions over 40 – 50 mm: “hot” pull-back with tandem brachytherapy regions

76 year old male with recurrent angina and found to have multifocal ISR of most of the RCA, successful revascularized with angioplasty. Total target length 75 mm. Distal vessel diameter 2.8 mm treated to 18.4 Gy at 2 mm depth. Proximal vessel diameter 3.4 mm treated to 23 Gy at 2 mm depth.

RCA angiogram pre-angioplasty

Distal RCA treated first

Proximal RCA treated second after “hot pull-back” under fluoro

Challenging Clinical Scenarios: bifurcation lesions

69 yo female with unstable angina found to have left main coronary bifurcation ISR. After angioplasty, there was a 10 mm injury length in proximal LCx and 20 mm injury length in proximal LAD. Both vessels had diameters < 3 mm and both treated with 40 mm Sr/Y-90 source train for 18.4 Gy at 2 mm depth.
Coronary Brachytherapy

- Brachytherapy in 760 hospitals by end of 2002
- 25,000 procedures in 2001
- 40,000 estimated for 2002

- Virtually disappeared when DES entered the field, except at a few tertiary care hospitals

- Currently, 5-10% of patients still have refractory ISR despite DES usage
- Currently, there are 41 medical centers actively using the Novoste BetaCath brachytherapy device in USA

- **AND......... coronary brachy is back!!!!!!**