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

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Other key Yale team members
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Coronary Brachytherapy:

nothing to declare.

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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

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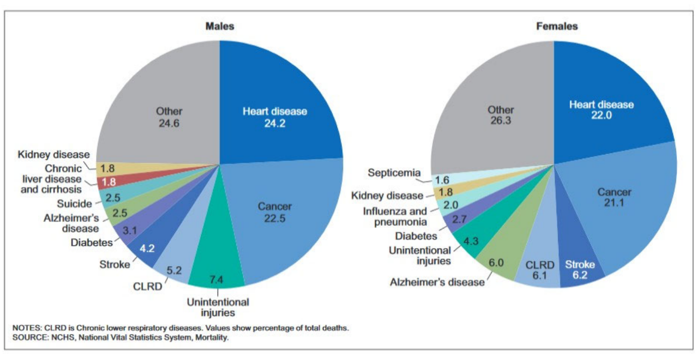
Coronary Artery Disease

- 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



Percent distribution of the 10 leading causes of death, by sex: United States, 2016

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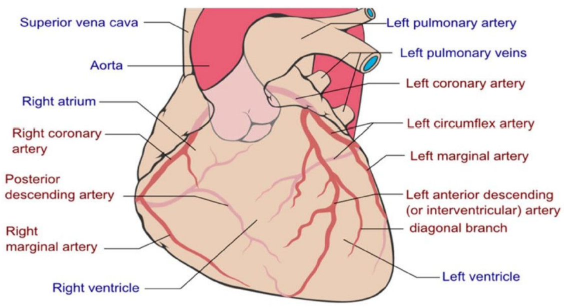
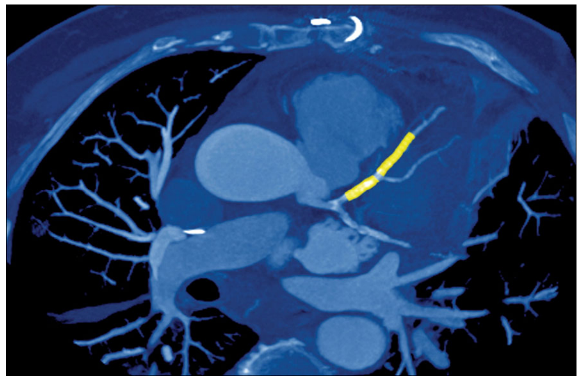
A Brief Introduction to Cardiac Anatomy





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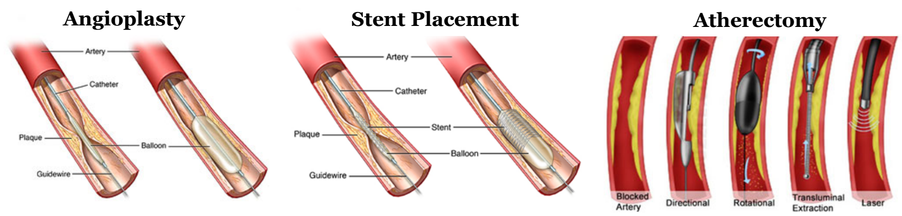
Coronary Artery Disease

- 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.



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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

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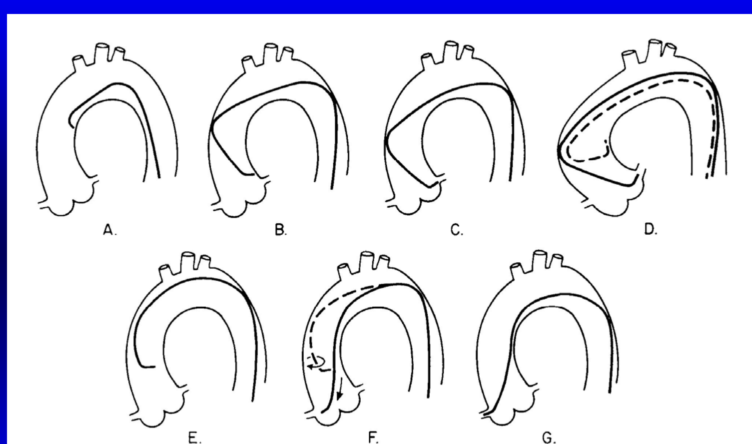

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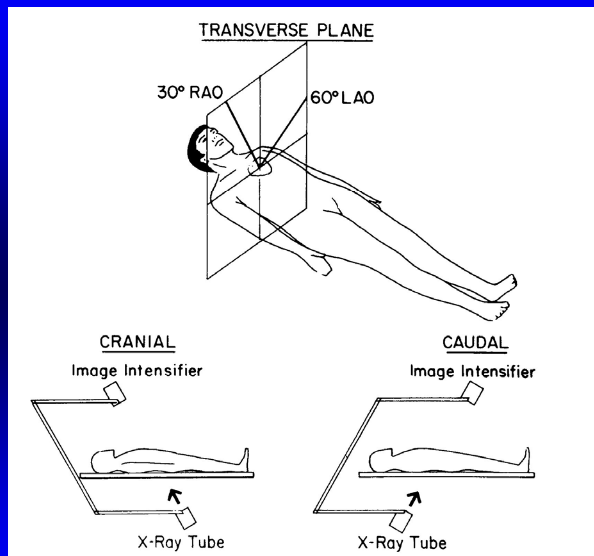

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Left Coronary Artery

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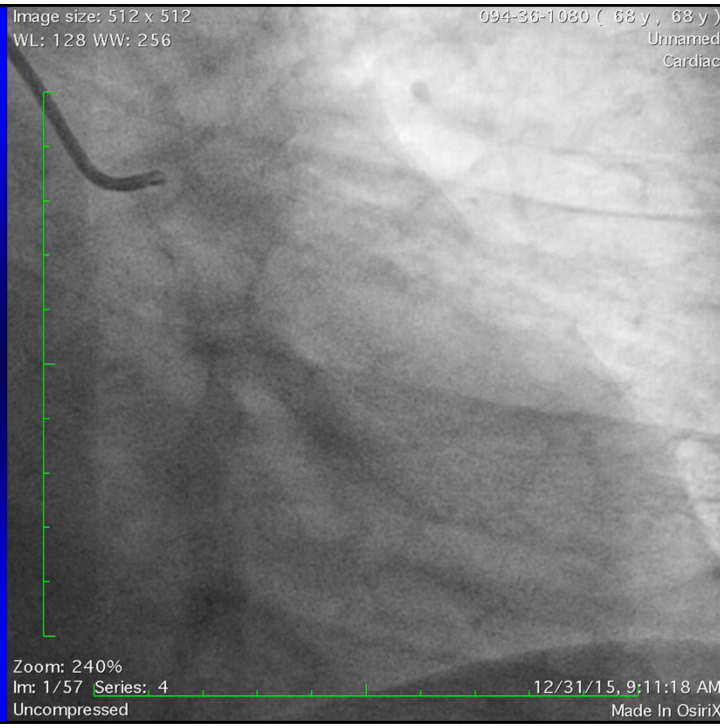

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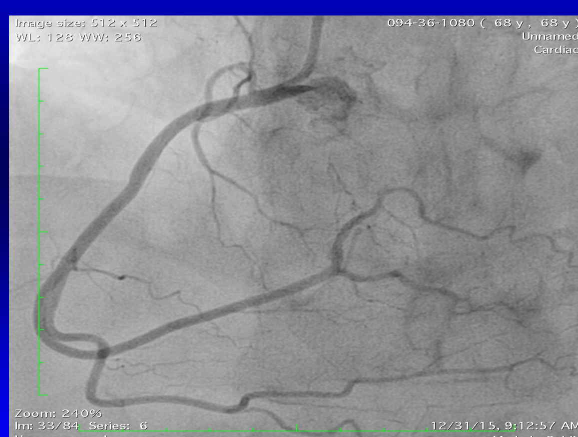
Right Coronary Artery



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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

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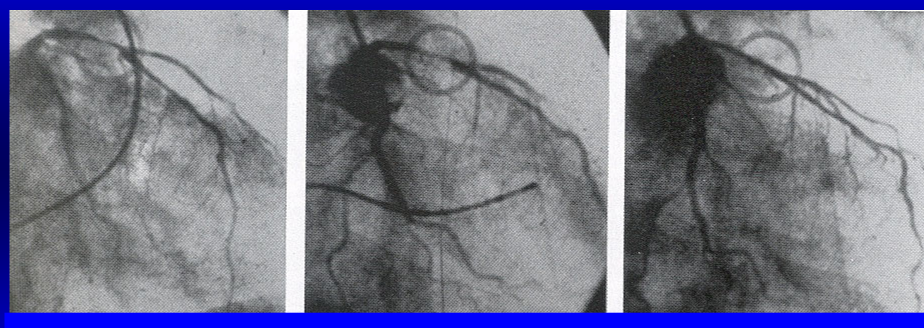
First PTCA, Gruentzig. Zurich Sept 1977, with 10 year (and later 23 year) follow-up



IV heparin, dextran, and aspirin for 3 days

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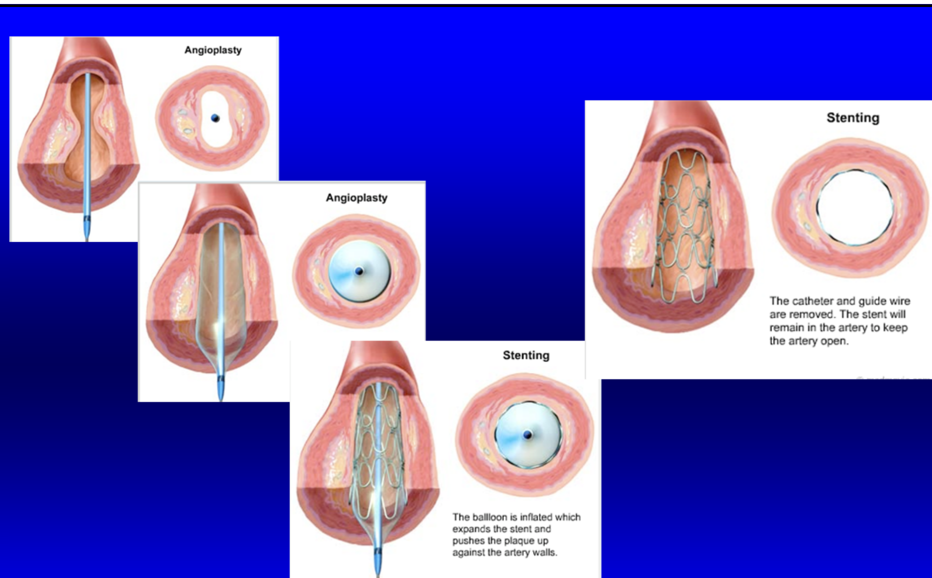

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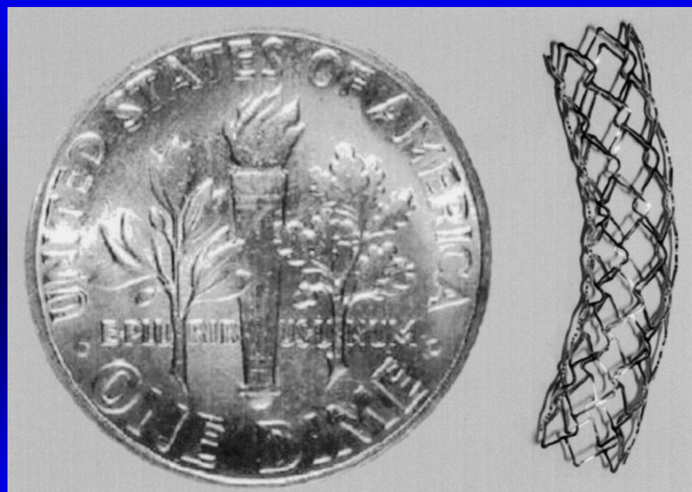
Size of an expanded coronary stent in relation to a dime



Dangas, G. et al. Circulation 2002;105:2586-2587

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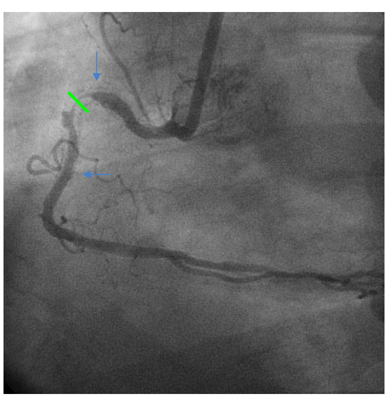
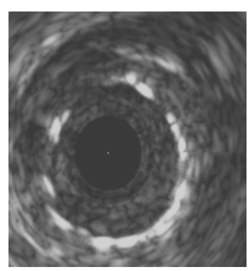
Neo-Intimal Hyperplasia – "In-stent" Restenosis





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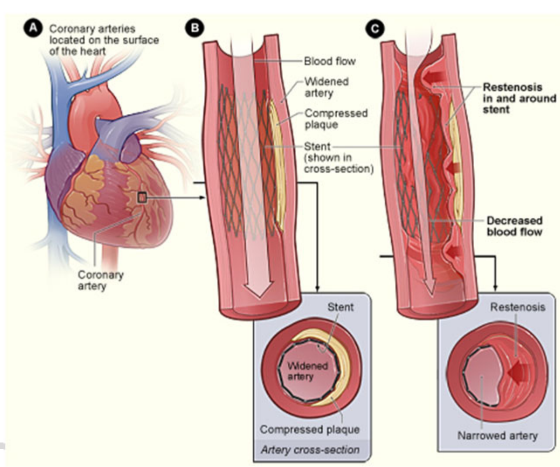
Clinical factors: High risk subgroups for ISR

- 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

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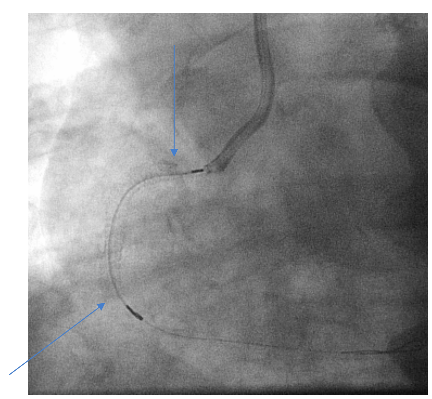
Coronary Brachytherapy - Workflow

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

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

3. Radioactive source train placed into the target coronary within catheter, position verified by fluoroscopy



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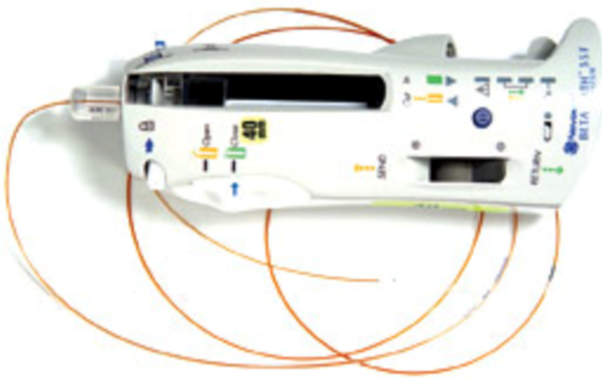
Novoste Beta-Cath – Sr90/Y90 source system



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

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Brachytherapy Team (Mandated by FDA Regulation)

- Interventional cardiologist
- Radiation oncologist
- Medical physicist
- Radiation safety officer

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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

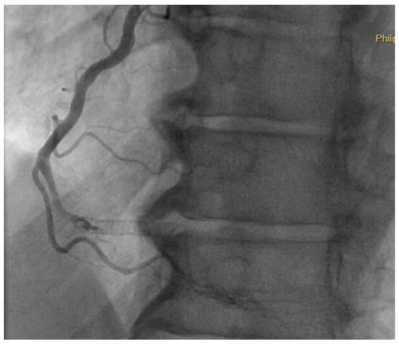
6. Dwell time from look-up table

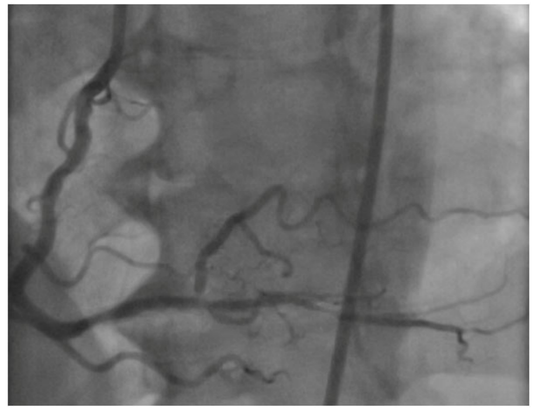
Recurrent ISR – Interventional Approach

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

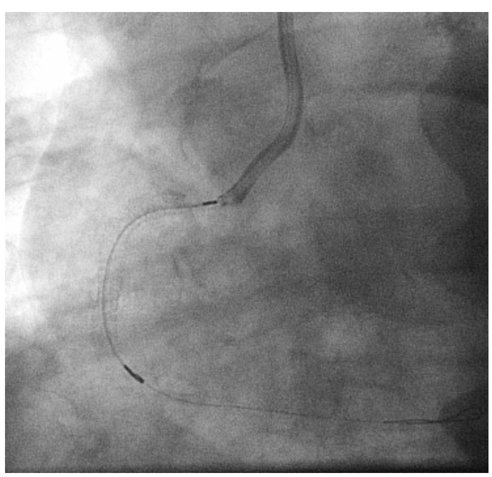
Recurrent ISR – Interventional Approach

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

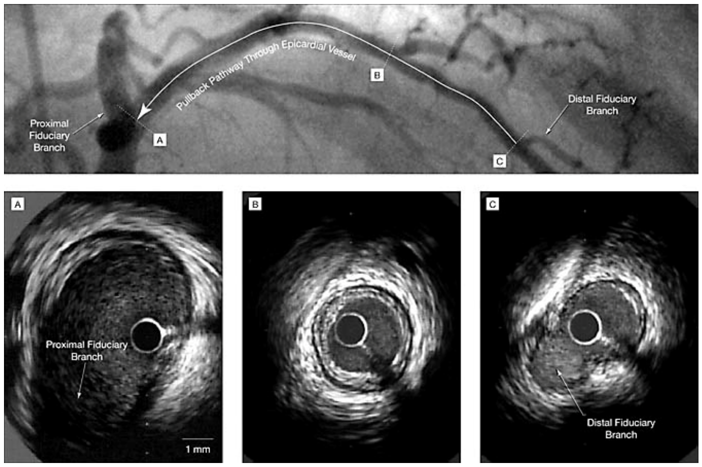




Angiographic view of BetaCath source train in RCA



Method of Intravascular Ultrasound (IVUS) Interrogation



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

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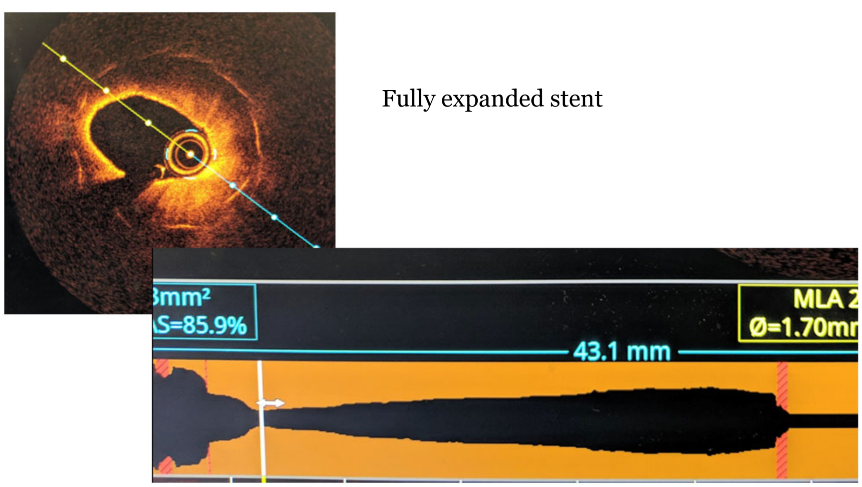
Restenosis



Fully expanded stent

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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

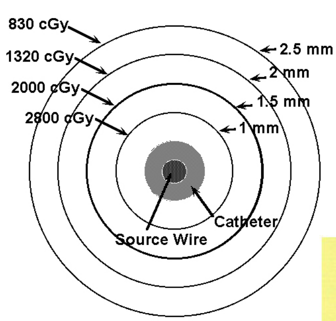
Isotopes Used in Intravascular Brachytherapy

Isotope	Emission	Half-life	Energy in MeV Avg	Max
^{192}Ir	Gamma	74 days	0.37	0.67
^{32}P	Beta	14 days	0.69	1.7
^{90}Sr	Beta	28 years	0.20	0.5
^{90}Y	Beta	64 hours	0.90	2.3

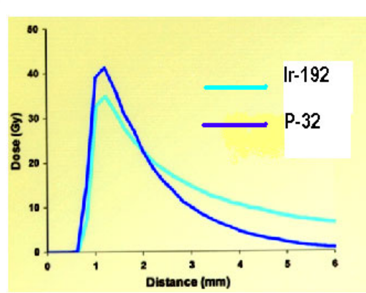
Beta and Gamma Radiotherapy

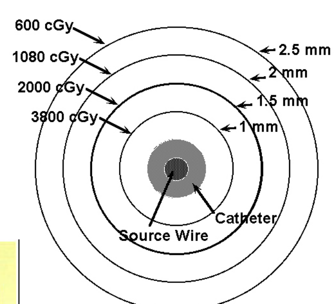
Beta:	Gamma:
Negligible rad safety concerns, less shielding	higher energy = more patient/staff exposure, need for more shielding
Poorer depth dose and target dose homogeneity	Better depth dose
shorter delivery time (2-10 min)	longer delivery time (15-30 min)
concerns about efficacy in larger vessels	broader spectrum of vessel sizes

Depth-dose for Beta and Gamma sources



Ir-192





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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

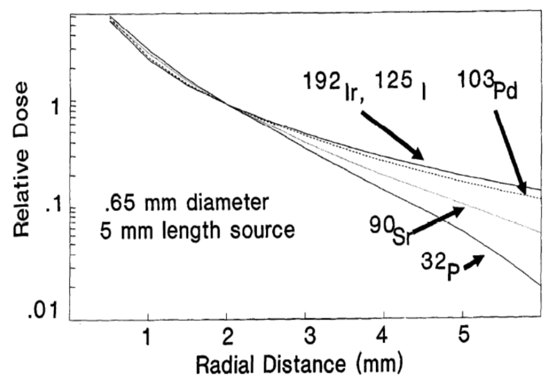

Fig. 1. Radial dose vs. distance for ^{192}Ir, ^{125}I, ^{103}Pd, ^{32}P, and ^{90}Sr. Sources are 0.65 mm diameter and 5.0 mm length. Doses have been normalized to 1.0 at a radial treatment distance of 2.0 mm.

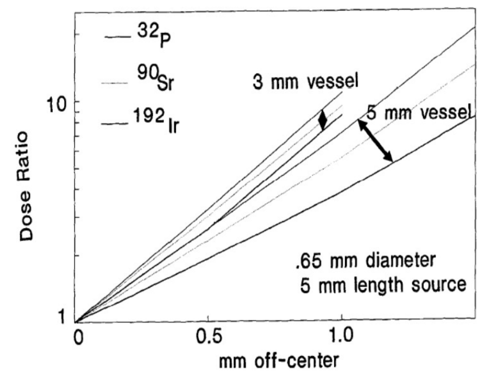

Fig. 3. Dose asymmetry (defined as maximum/minimum dose to vessel wall) resulting from inaccurate centering of 5 mm long ^{192}Ir, ^{32}P, and ^{90}Sr sources within arteries of 3 and 5 mm diameter. When the source is centered in the artery, the dose asymmetry is 1.0.

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Radiation Dose perturbations from stents and calcifications

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

Pei Fan[a], Sou-Tung Chiu-Tsao[a,*], Neil Suresh Patel[a], Allen Shih, Kumar Ravi[a], Warren Sherman[a], Hung-Sheng Tsao[b], Julianna Pisch[a], and Louis B. Harrison[a]

Cardiovascular Radiation Medicine 2 (2000) 18–25

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-emmitters

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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

TRIAL		Source
SCRIPPS I	Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting	Ir-192
WRIST	The Washington Radiation In-Stent Trial	Ir-192
LONG WRIST		Ir-192
SVG WRIST		Ir-192
BETA WRIST	-	Sr-90/Y-90
BERT	Beta Energy Restenosis Trial	Sr-90
PARIS	Peripheral Artery Radiation Investigative Study	Ir-192
Beta-Cath & START	Beta-Cath Trials	Sr-90/Y-90
ARREST	Angiorad Radiation for Restenosis Unstented native Vessel	Ir-192
PREVENT	perliferation Reduction with Vascular Energy Trial	P-32
Gamma-I		Ir-192

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

Leon M, et.al., N Engl J Med 2001; 344:250-256

GAMMA-1

	IRT (%)	Placebo (%)	P value
6 mo restenosis*	32.4	55.8	0.01
In-stent	21.6	50.5	0.005
TLR at 9 mo	24.4	42.1	<0.01
MACE 9 mo	28.2	43.8	0.02
Late thrombosis	5.3	0.8	0.07

Leon NEJM, 2001

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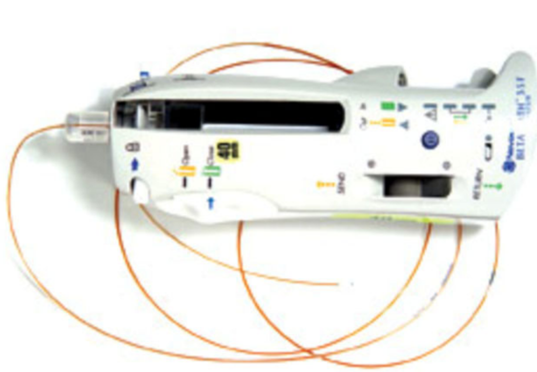
Novoste Beta-Cath – Sr90/Y90 source system



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

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START – pivitol trial of BetaCath system for ISR, pre-DES era

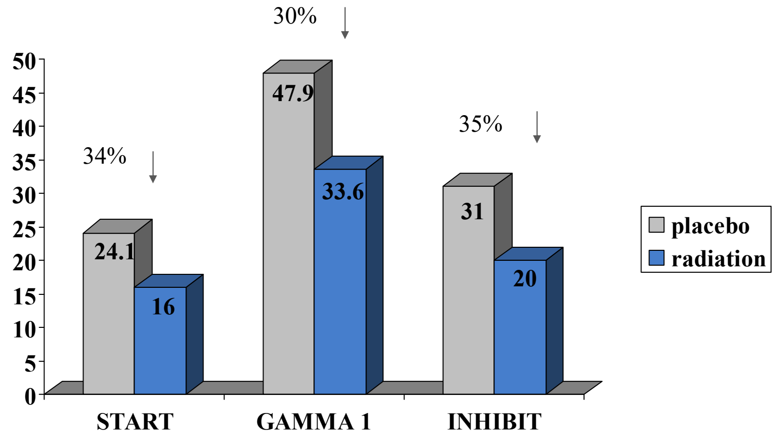
- Randomized, double-blinded, multicenter
- 476 patients with in-stent restenosis
- 8 month angiographic follow-up
- 18.4 or 23 Gy at 2mm depth from Sr^{90}/Y^{90} source based on mean luminal diameter threshold of 3.4 mm
- Hydraulic delivery system.

START -- Results

	IRT (%)	Placebo (%)	P value
8 mo restenosis	24.4	45.9	<0.001
In-stent	14.2	41.2	<0.001
TLR at 8 mo**	17	26.8	0.015
MACE at 8 mo	19.1	28.7	0.024

Popma, Circulation 2002

Target Vessel Revascularization



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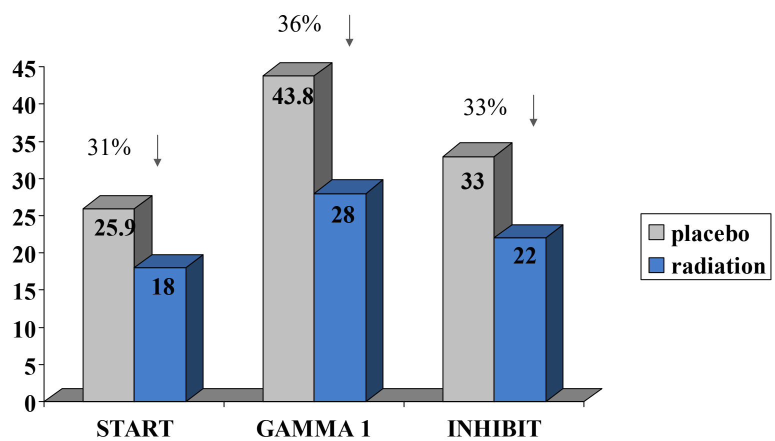
MACE



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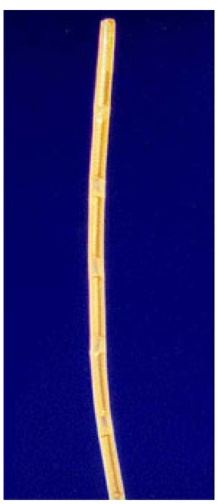
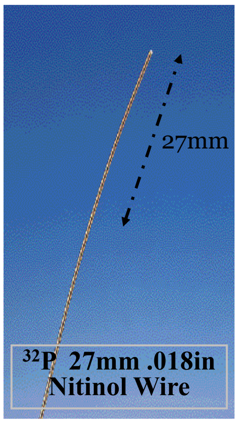
FDA Approved Systems: Clinical Indications and Usage

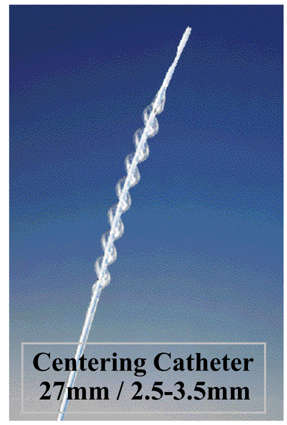
	Novoste BetaCath™	Cordis Checkmate™	Guidant Galileo™
Lesion Type	In-stent restenosis in native coronary artery	In-stent restenosis in native coronary artery	In-stent restenosis in native coronary artery
Lesion Length	"Treatable with 20 mm balloon"	Up to 45 mm	Up to 47 mm
Vessel diameter	2.7 – 4.0 mm	2.75 – 4.0 mm	2.4 – 3.7 mm
Source	Beta ($^{90}Sr/^{90}Y$)	Gamma (^{192}Ir)	Beta (^{32}P)
Contra-indications	Cannot take antiplatelet or anticoagulant	Cannot take antiplatelet or anticoagulant	Cannot take antiplatelet of anticoagulant

FDA Approved Brachytherapy Systems Gamma: Cordis CheckMate™



FDA Approved Brachytherapy Systems Guidant: Galileo™ System





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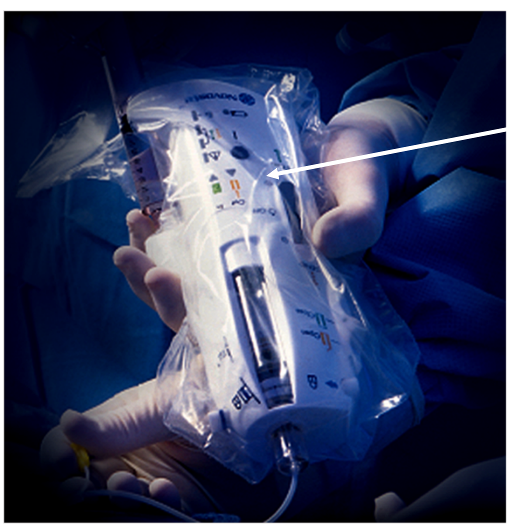
FDA Approved Brachytherapy Systems Beta: Novoste BetaCath™



Transfer device using
hydraulic delivery
of the source train

Delivery Catheter
3-lumen, closed end

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Radiotherapy-Adverse Effects

- **"Edge effects"**
- Late thrombotic occlusion
- Long-term effects

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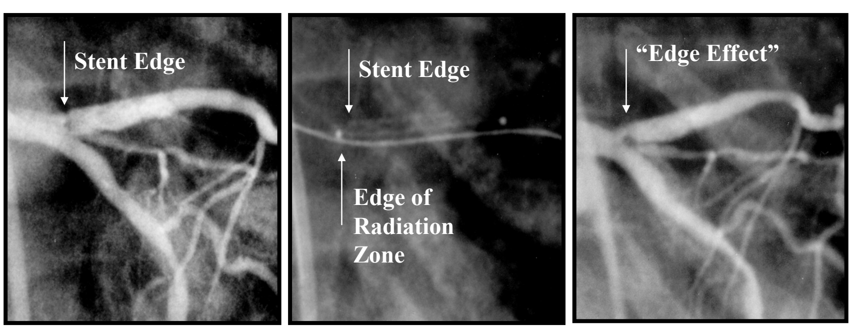
"Edge Effect"

- •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**

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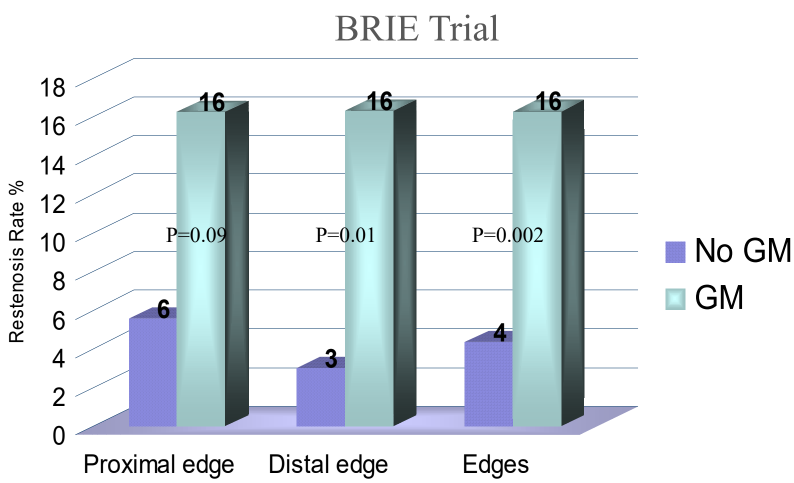
Geographic Miss (GM) and Likelihood of Edge Restenosis



Geographic miss is the primary cause of edge restenosis

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Radiotherapy-Specific Effects

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

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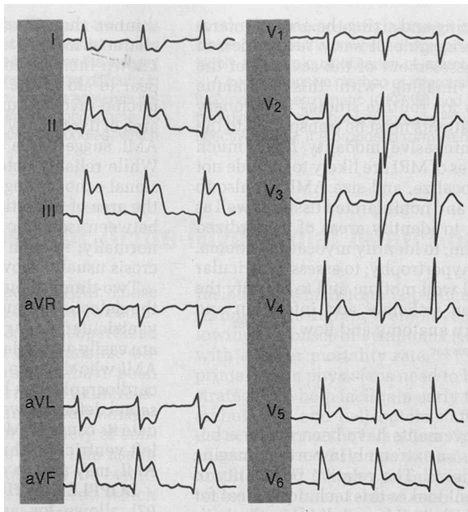
Late (>30 d) Thrombotic Events After Vascular Brachytherapy



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

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

Trial	Months of Ticlid/Plavix	% New Stents	Months of F/U	Late Thrombosis
SCRIPPS III	6	26%	6	0%
WRIST Plus	6	29%	6	0%
START	3	21%	9	0%
INHIBIT	6	28%	9	1%

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Radiotherapy-Specific Effects

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

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Coronary Brachytherapy

- Brachytherapy is an effective treatment for in-stent restenosis
- Mid-term (3-5 yr) safety established
- Efficacy maintained in highest risk subgroups

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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

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Presented at ACC 2006

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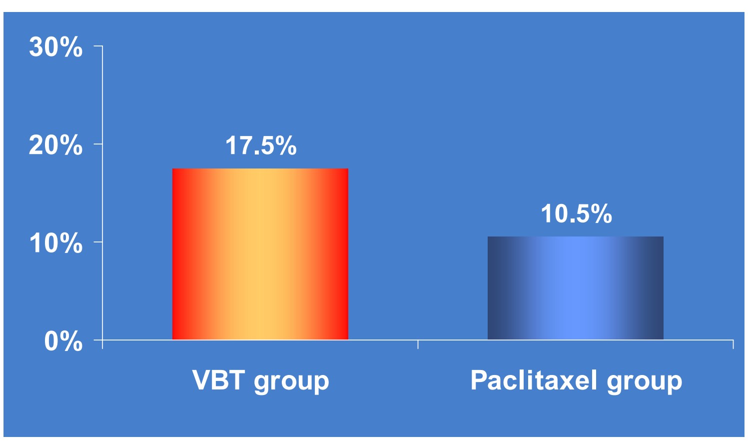
TAXUS V ISR Trial: Primary Endpoint

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)**

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Presented at ACC 2006

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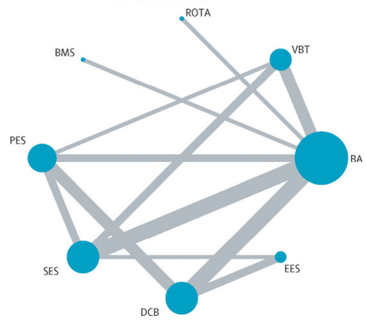
What are the Rx options for DES-ISR?

Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis

George C M Siontis, Giulio G Stefanini, Dimitris Mavridis, Konstantinos C Siontis, Fernando Alfonso, María J Pérez-Vizcayno, Robert A Byrne, Adnan Kastrati, Bernhard Meier, Georgia Salanti, Peter Jüni, Stephan Windecker

Lancet 2015; 386: 655-64

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



**** but IVBT not well studied after DES ISR**

	Year	Type of ISR	Interventions	Sample size (control/ intervention)	Follow-up (months)	
					Angiographic	Clinical
VBT						
Gamma-1	2001	BMS	BA vs VBT	252 (121/131)	6	9
START	2002	BMS	BA vs VBT	476 (232/244)	8	24
Reynen et al	2006	BMS	BA vs VBT	165 (78/78)	6	12
ROTA						
ARTIST	2002	BMS	BA vs ROTA	298 (146/152)	6	6
ROSTER	2004	BMS	BA vs ROTA	200 (100/100)	6-9	12
BMS						
RIBS	2003	BMS	BA vs BMS	450 (226/224)	6	52
Ragosta et al	2004	BMS	BA vs BMS	58 (29/29)	NA	9
Ragosta et al	2004	BMS	ROTA vs BMS	55 (30/25)	NA	9
Alfonso et al	2005	BMS	BA vs BMS	40 (20/20)	6	24
DES						
ISAR-DESIRE	2005	BMS	BA vs PES vs SES	300 (100/100/100)	6	12
RIBS-II	2006	BMS	BA vs SES	150 (74/76)	9	38
SISR	2006	BMS	VBT vs SES	384 (125/259)	6	60
TAXUS V ISR	2006	BMS	VBT vs PES	396 (201/195)	9	24
Schukro et al	2007	BMS	VBT vs PES	37 (17/20)	6	6
INDEED	2008	BMS	VBT vs SES	129 (64/65)	6	12
ISAR-DESIRE 2	2010	DES	PES vs SES	450 (225/225)	6-8	12
CRISTAL	2012	DES	BA vs SES	197 (61/136)	12	12
Song et al	2012	DES	BA vs SES	96 (48/48)	9	12
Song et al	2012	DES	SES vs EES	66 (32/34)	9	12
RIBS V	2014	BMS	DCB vs EES	189 (95/94)	9	12
RIBS IV	2015	DES	DCB vs EES	309 (154/155)	9	12
DCB						
PACCOCATH-ISR I and II	2006 (I)-2008 (II)	BMS and DES	BA vs DCB	108 (54/54)	6	60
PEPCAD II	2009	BMS	PES vs DCB	131 (65/66)	6	12
Habara et al	2011	DES	BA vs DCB	50 (25/25)	6	6
PEPCAD-DES	2012	DES	BA vs DCB	110 (38/72)	6	6
Habara et al	2013	BMS and DES	BA vs DCB	210 (72/138)	6	6
ISAR DESIRE 3	2013	DES	BA vs PES vs DCB	402 (134/131/137)	6-8	12
PEPCAD China ISR	2014	DES	PES vs DCB	215 (106/109)	9	12

What are the results of IVBT post-DES ISR?

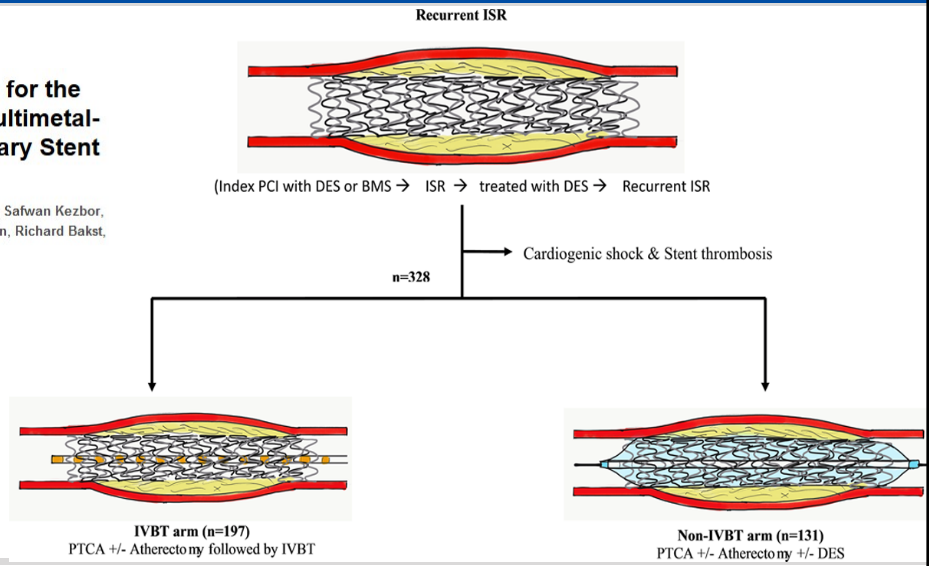
Limited numbers of retrospective trials,

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

Mt Sinai series – DES-ISR-IVBT – Circ Cardiovasc Interv 2018

Intravascular Brachytherapy for the Management of Repeated Multimetal-Layered Drug-Eluting Coronary Stent Restenosis

Mithun J. Varghese, Samit Bhatheja, Usman Baber, Safwan Kezbor, Aditi Chincholi, Surbhi Chamaria, Michael Buckstein, Richard Bakst, Annapoorna Kini, and Samin Sharma



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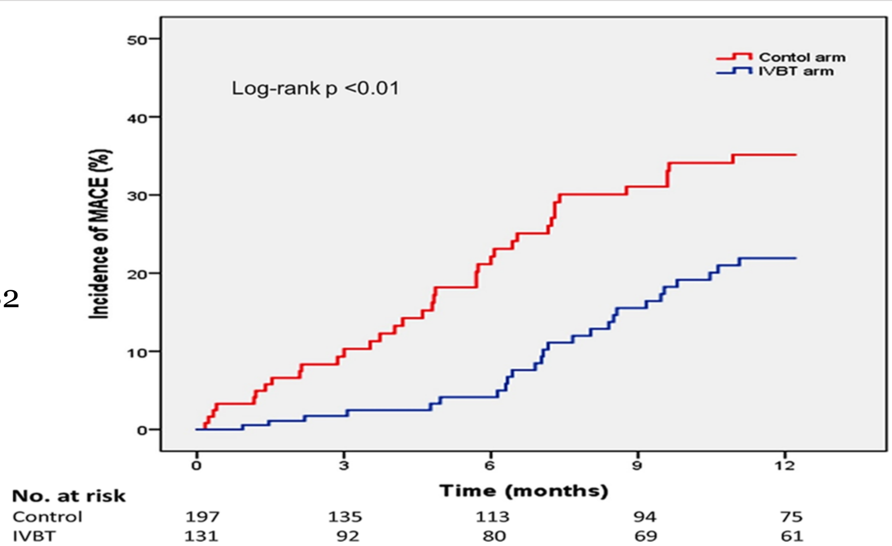
Mt Sinai series – DES-ISR-IVBT – Circ Cardiovasc Interv 2018

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



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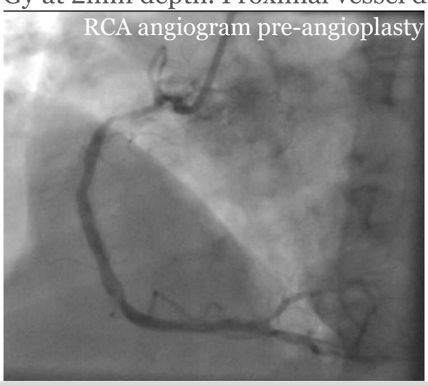
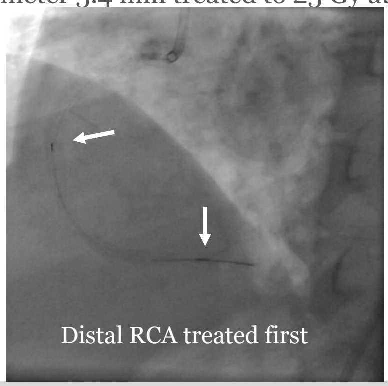
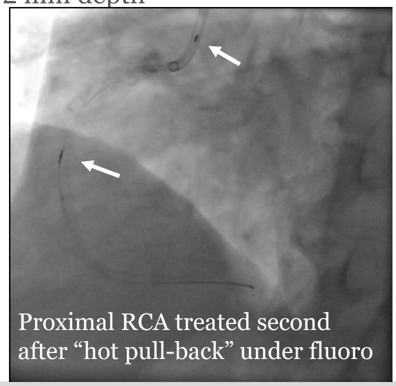
Challenging Clnical Scenarios: reRx and long lesions

- 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 2mm depth. Proximal vessel diameter 3.4 mm treated to 23 Gy at 2 mm depth







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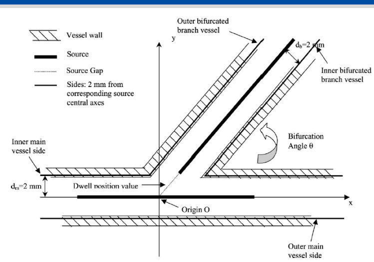
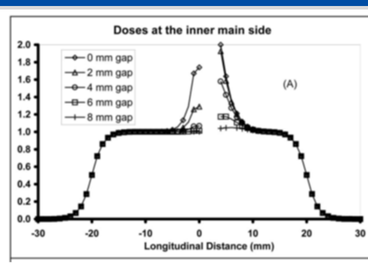
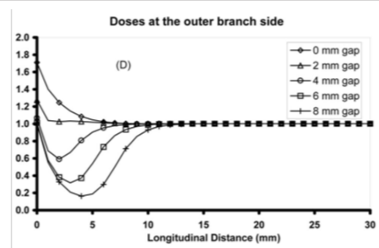
Challenging Clnical Scenarios: bifurcation lesions

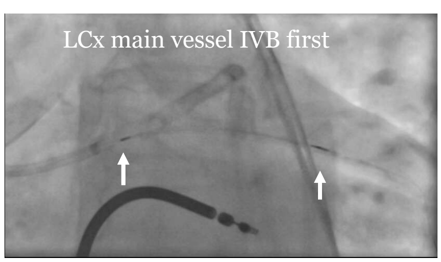


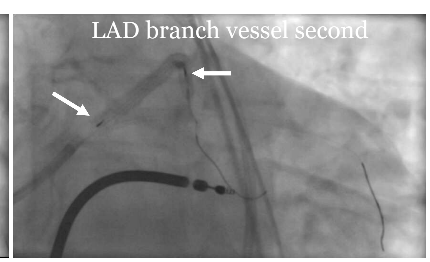




Yue, et.al. Medical Physics 30:1628, 2003 and 31:2610, 2004

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 a 2 mm depth





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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!!!!!!**