MHIF Research Highlights: APRIL 2020

RESEARCH HIGHLIGHTS IN THE NEWS

Dr. Steven Bradley was interviewed for Twin Cities Public Television's (TPT) *Coronavirus – An Almanac Special* on April 17
Follow MHIF on social media or visit tpt.org/Almanac/ to see the full episode

Dr. Santiago Garcia was interviewed by Health News Daily and quoted in a story published in *U.S. News & World Report*
Is COVID-19 Causing More People to Suffer Heart Attacks at Home?

Interested in MHIF Updates During COVID-19?
Visit mplsheart.org/coronavirus/

MHIF FEATURE:

HemoLung Emergency Use of ECCO2R
Dr. Saavedra-Romero

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Carina Benson - carina.benson@allina.com

MHIF Research Tiger Team ready to support HemoLung with 24/7 onsite research coverage!

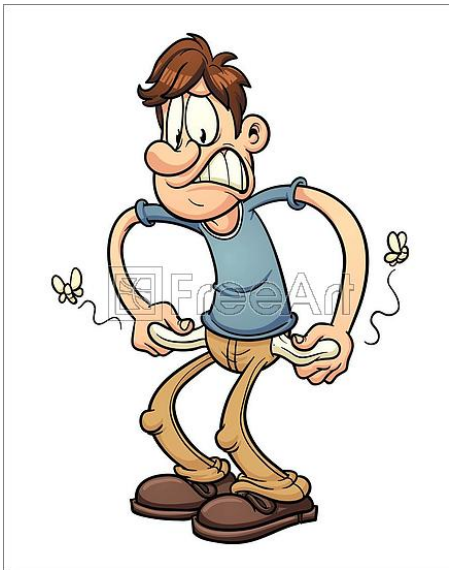
Carina Benson, Jake Jensen, Andrew Nauertz, Alyssa Taffe, Lisa Tindell, Kari Williams

Vascular brachytherapy, the rise of the Phoenix

Michael Megaly, MD, MS

April 20th, 2020

Still no disclosures!!



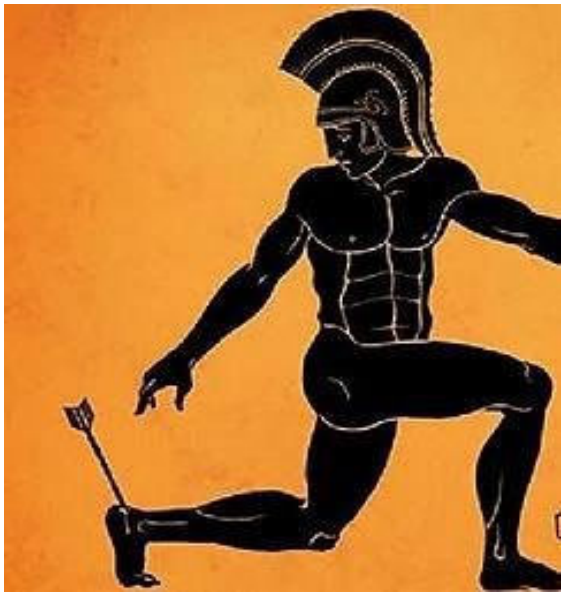
Objectives

1- What is recurrent (resistant) in-stent restenosis?

2-Vascular brachytherapy; mechanism, outcomes, and current use

3-Future directives

In-stent restenosis (ISR)



Not only important for interventional cardiologists

Major limitation

Understand options of treatment

Restenosis

- **Lumen diameter reduction after PCI**
- **Angiographic diagnosis**

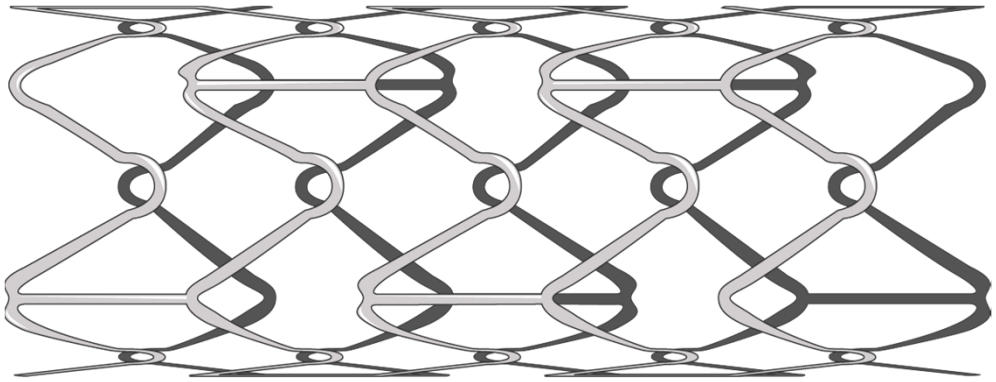
Target lesion revascularization (TLR) (revascularization of the same lesion)

- **1-Angiography driven (ISR >70%) or Ischemia driven (symptoms or stress test)**
- **2-TVR (target vessel revascularization) is revascularization of the same vessel.**

Pre-stent era
(32%-55%)

Stoker 2012 Circ Int
Stone 2004 NEJM
Stettler 2007 Lancet
Dangas 2010 JACC

BMS
17-44 % (2-5 years)



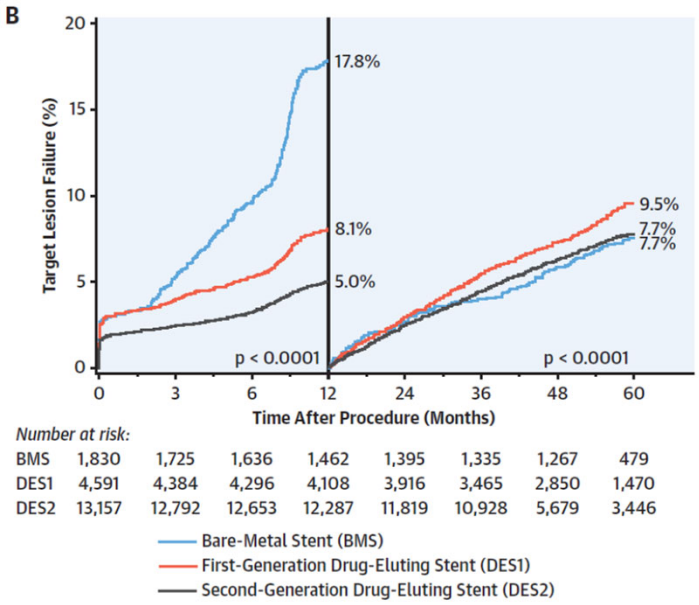
Stoker 2012 Circ Int
Stone 2004 NEJM
Stettler 2007 Lancet
Dangas 2010 JACC

DES

ISR up to 20%

TLR 2-6% at 1 year (and increasing)

10% of PCI in NCDR are for ISR



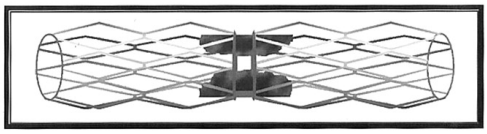
Madhavan 2020 JACC
Mousa 2018, Abstract ACC

Is it bad?

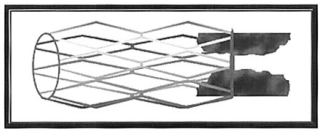
- Recurrence of angina symptoms
- Acute coronary syndrome (10%)
- Independently associated with 4-year **mortality** (Cassesse 2015, EHJ) 10,004 patients

Patterns

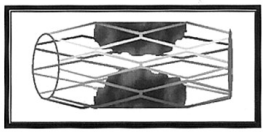
ISR Pattern I: Focal



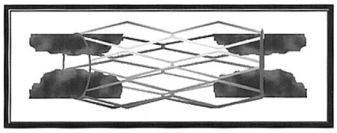
Type IA: Articulation or Gap



Type IB: Margin

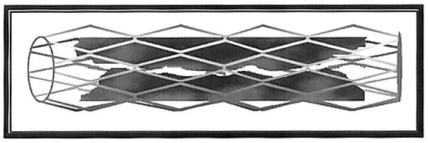


Type IC: Focal Body

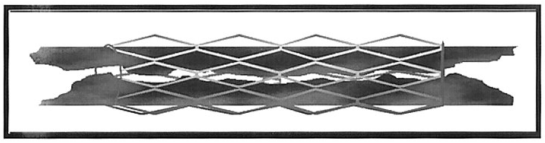


Type ID: Multifocal

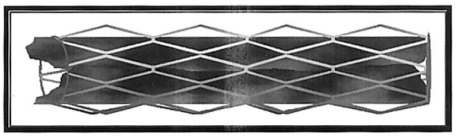
ISR Patterns II, III, IV: Diffuse



ISR Pattern II: Intra-stent



ISR Pattern III: Proliferative

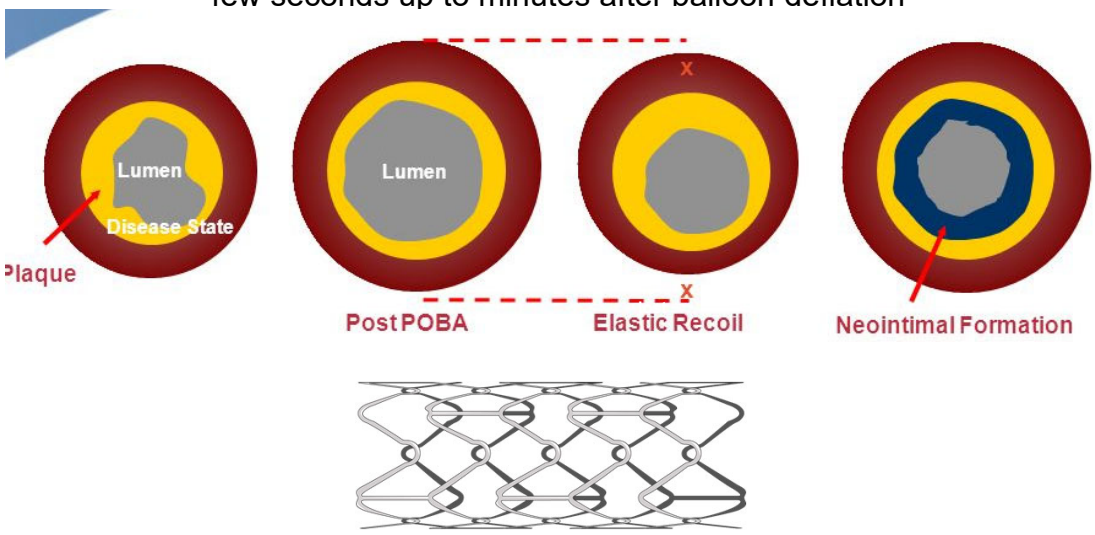


ISR Pattern IV: Total Occlusion

1-Elastic recoil

Elastin fibers

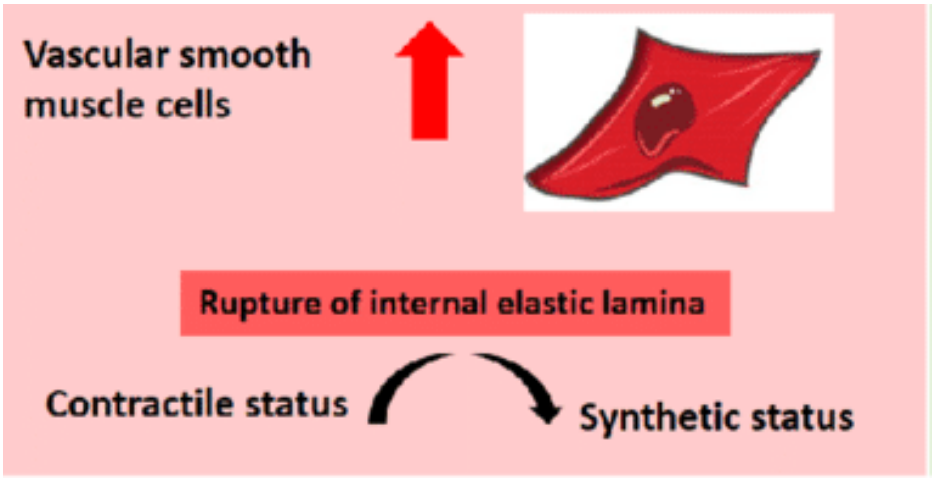
few seconds up to minutes after balloon deflation

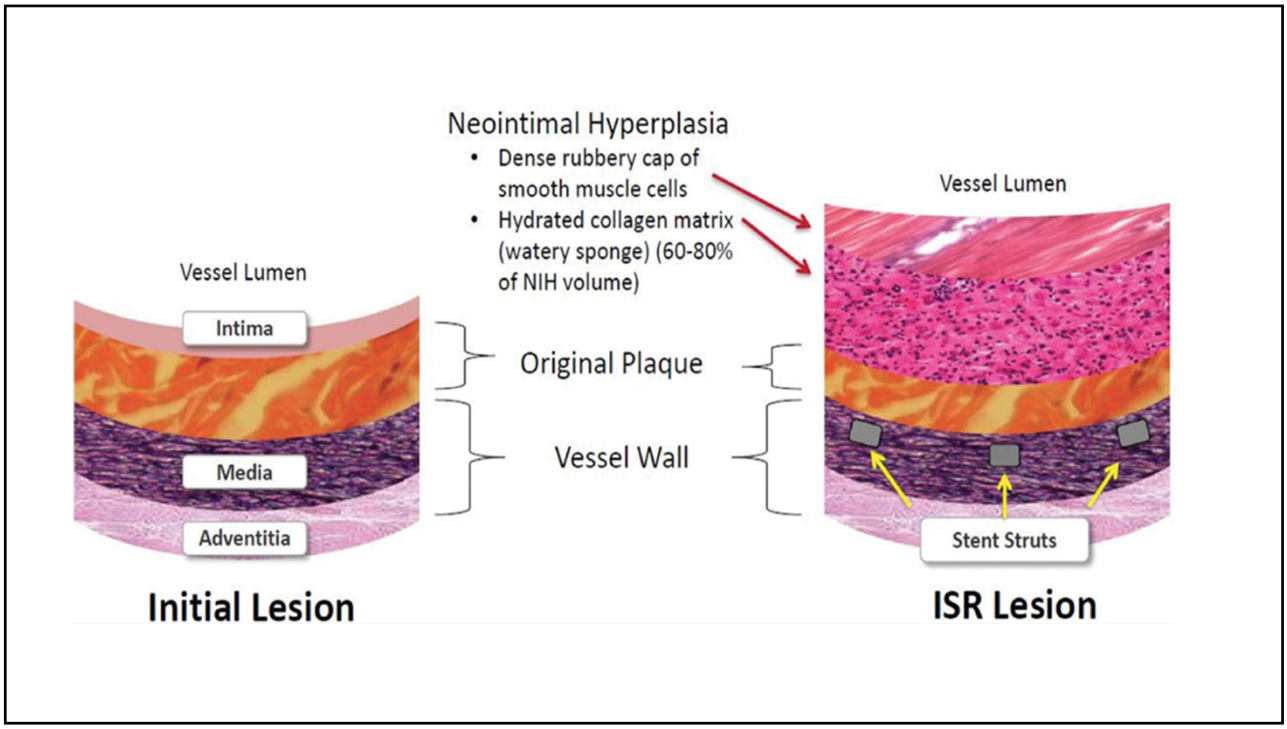


2-Vascular remodeling

Vessel injury

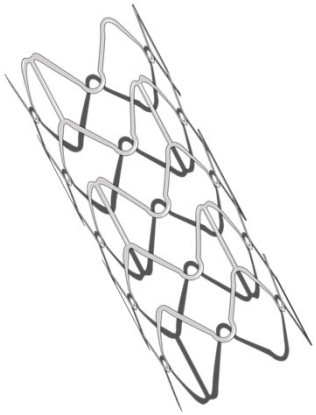
Vascular smooth muscle cell proliferation or migration and activation, mitogens and cytokines

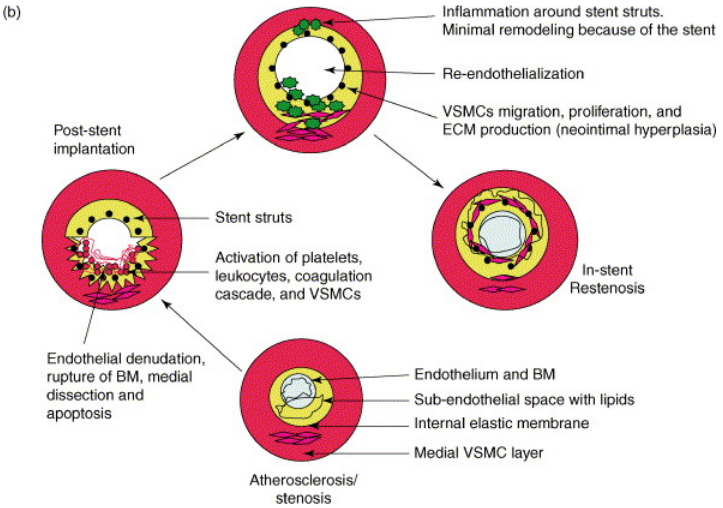




3-Inflammation by stent struts

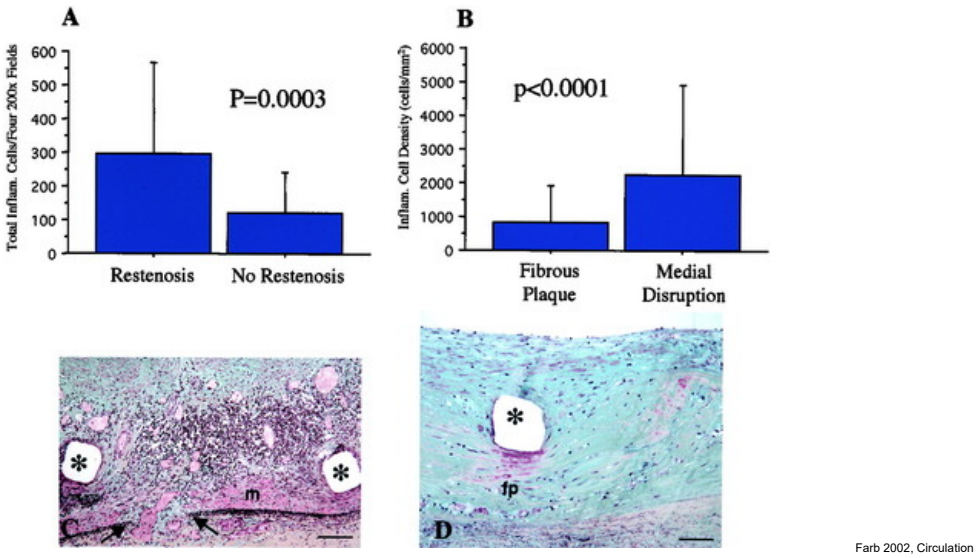
Injury, Inflammation, hypersensitivity, discontinuity of endothelium trapping blood elements





116 stented lesions (at least 90 days)→ postmortem detailed histological analysis

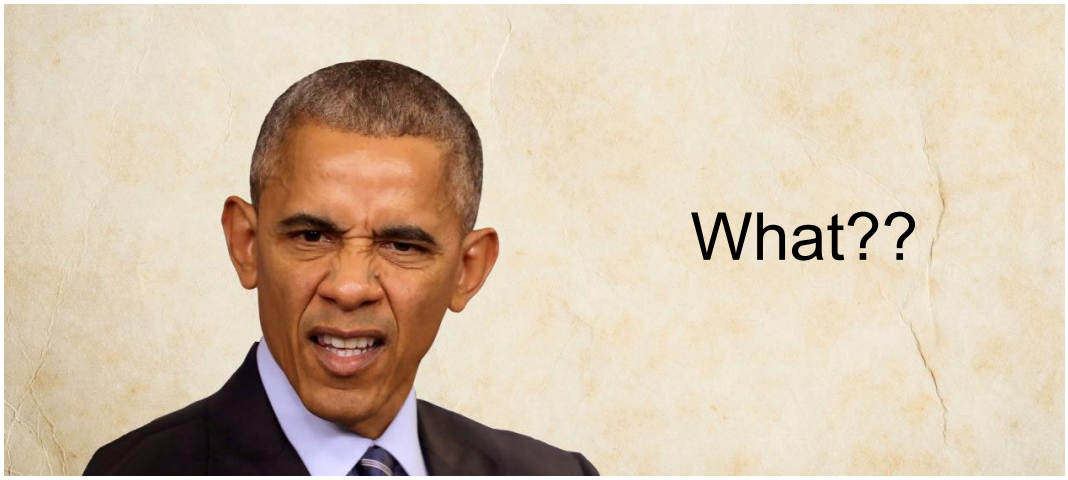
Greater accumulation of **inflammatory cells (2.4-fold increase) in restenosis lesions**



Farb 2002, Circulation

What else?

4-Neoatherosclerosis

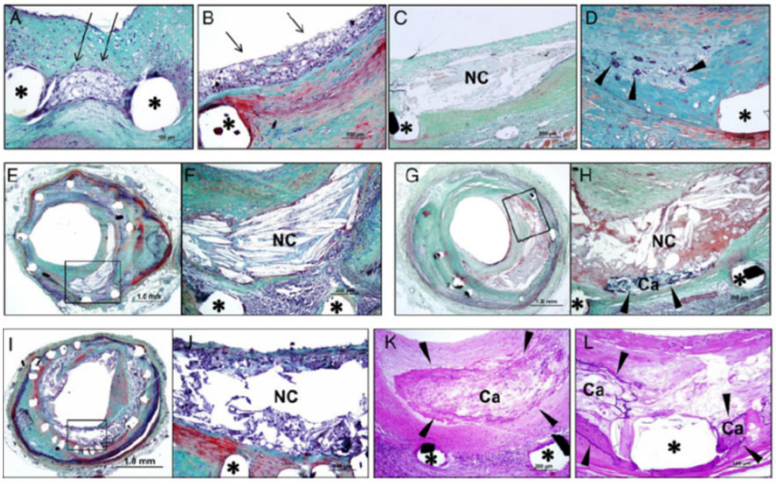


Atherosclerotic lesions affecting the neointima

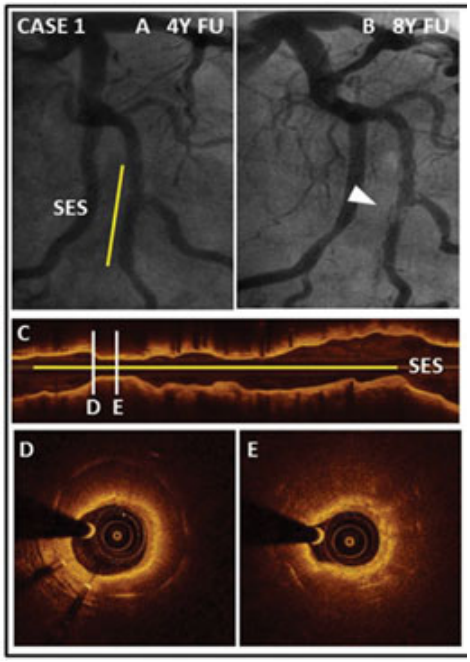
Can be calcific

Can occur at anytime (earlier in DES)

Correlated with late stent thrombosis



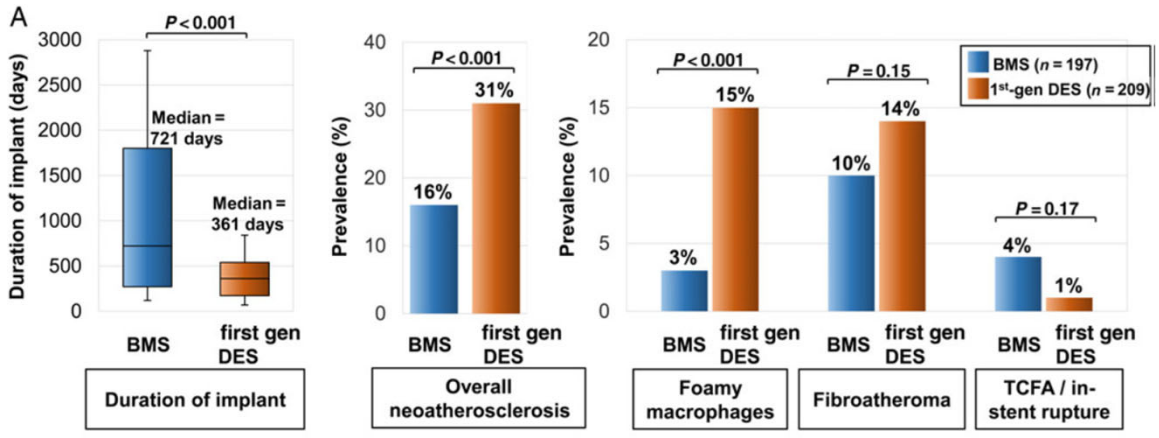
(Nakamura 2016 Circ Intv.)



Taniwaki 2014, EHJ

More frequent in DES and occurs earlier

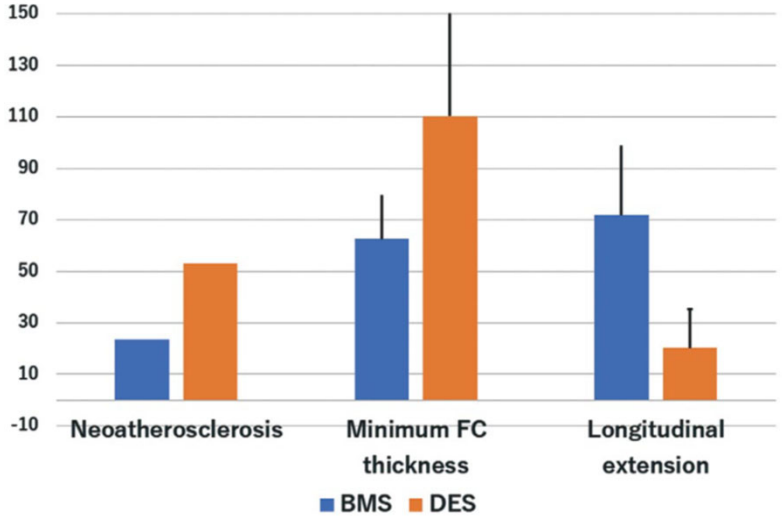
Autopsies of 406 stented vessels
DES mean 1.5 years; BMS median 6 years



Nakazawa 2011, JACC

Longitudinal extension is less in the DES and higher fibrous cap thickening

OCT of 98 lesions (1st gen DES neoatherosclerosis 68%, second gen DES 30%)



Nakamura 2019 Circulation J

Patients

Diabetes (IGF-1 induced neointimal hyperplasia)

Hemodialysis

Certain polymorphisms

Lesions

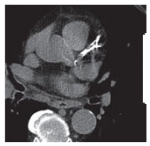
Inhomogeneous distribution of the drug calcification, tortuosity

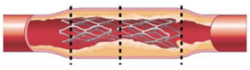
Underlying unstable lesion

Stent deployment problems (malapposition, underexpansion, edge dissection)

Long stents (>32 mm) Small stents (< 3 mm)

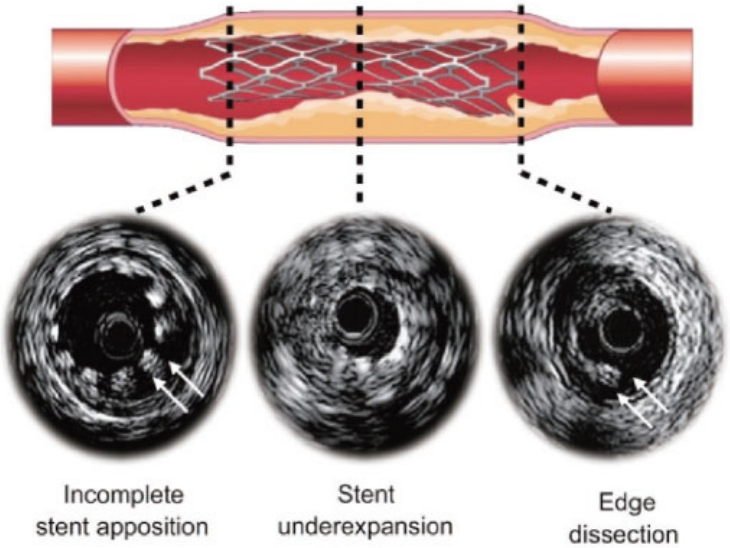
Stent fracture





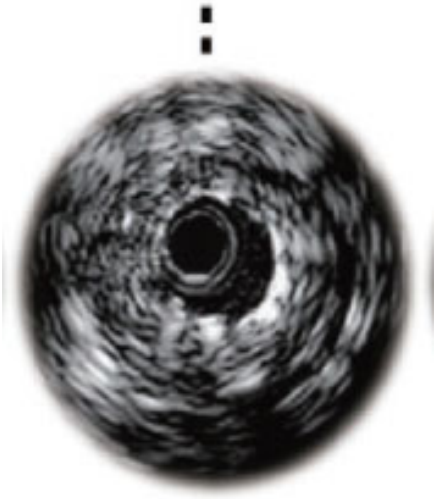
Choi 2014, AJC
Stone 2010, JACC
Costa 2010 JACC INT
Nakazawa 2011 JACC
Nebeker 2006 JACC

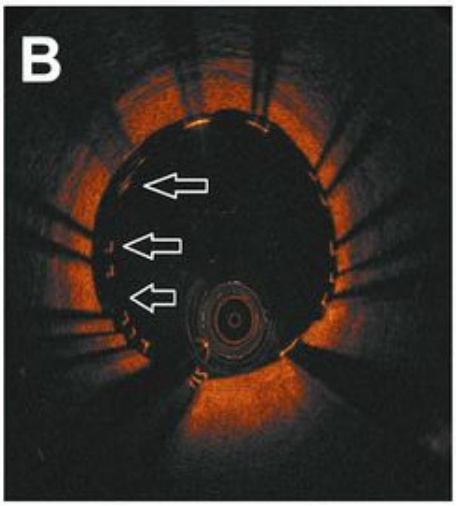
Stent deployment problems

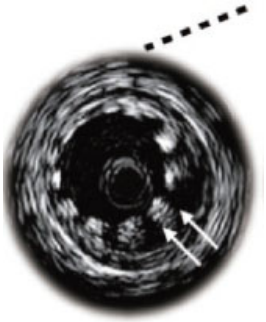


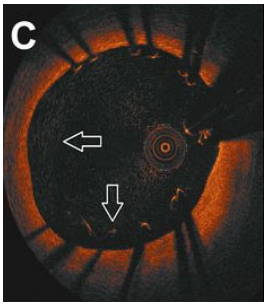
Stent under expansion

Minimum lumen area <90% of the average reference lumen area

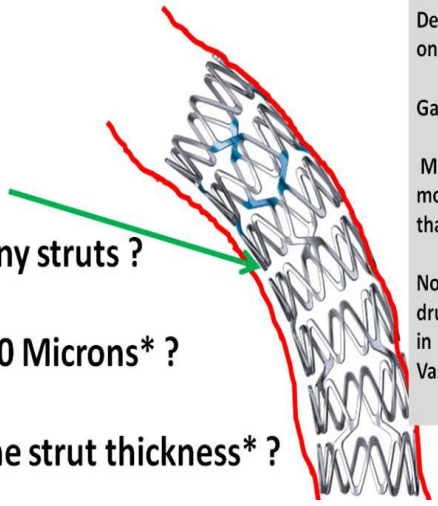








Mal-apposition



How many struts ?

200 Microns* ?

One strut thickness* ?

Detected by IVUS /OCT only

Gaps > 200 microns

Mal-apposition has more concern with DES than BMS.

Non contact zones lack drug delivery resulting in inhomogenous neo Vascularisation.

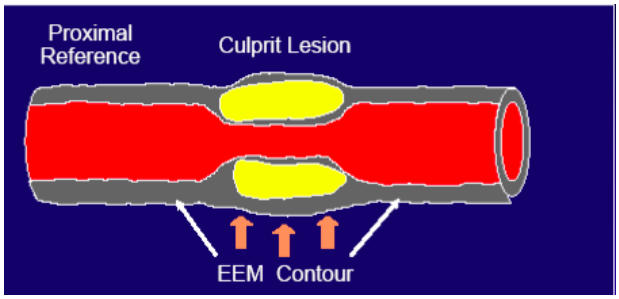
Late stent malapposition

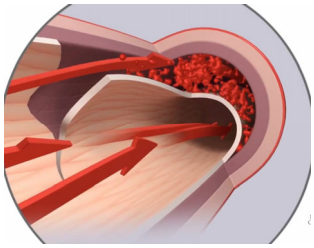
1-Positive remodeling of the vessel

2-Dissolution of the thrombus or partial regression of atherosclerotic plaque

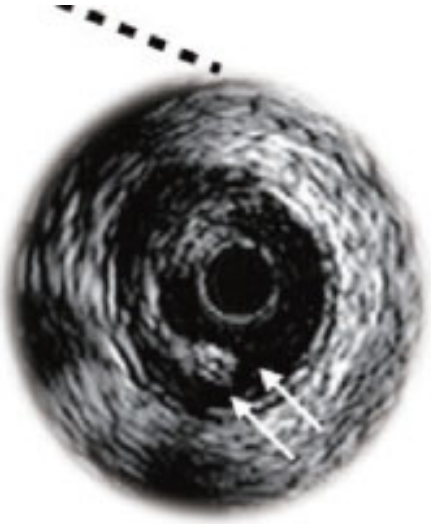
SCAD

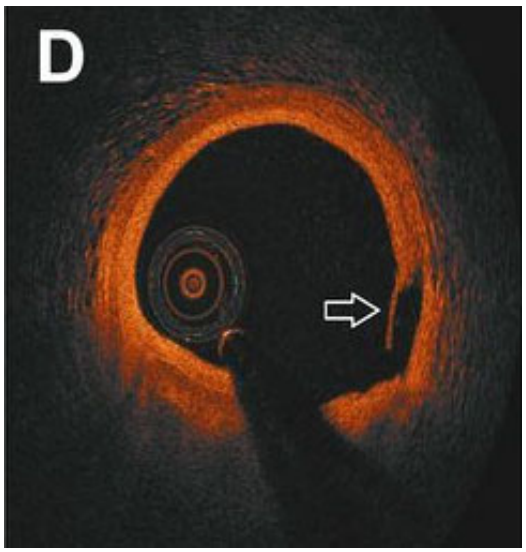
3-Chronic stent recoil.



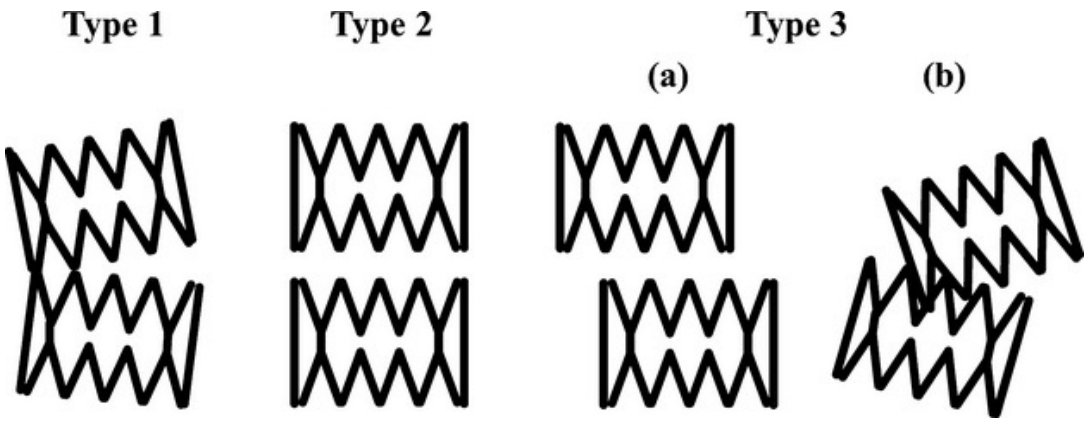


Edge dissection





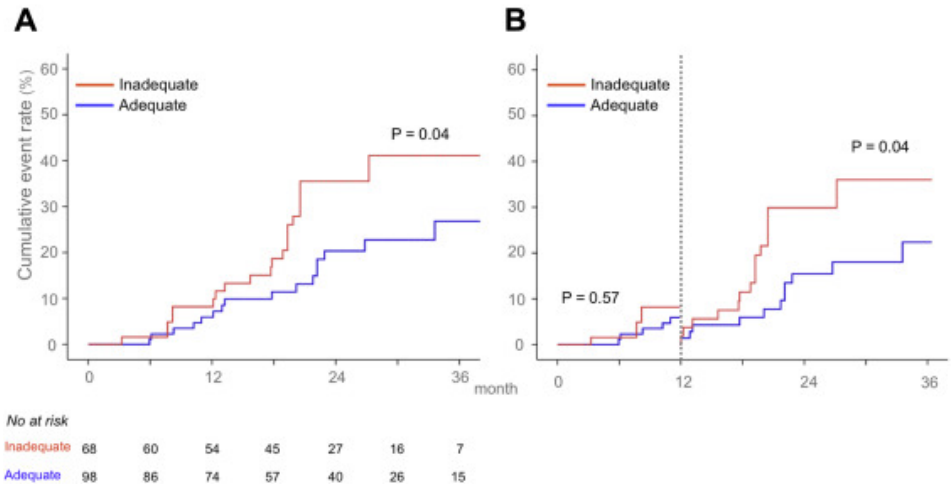
Stent fracture (1-8%)



Kuramitsu 2014 JAHA

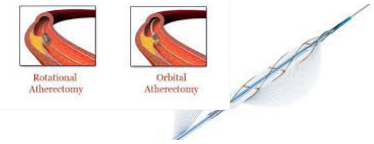
Residual stenosis or major neointimal dissection→ diffuse ISR→ **TLR**
(Tanaka 2016, JACC)

Target lesion revascularization

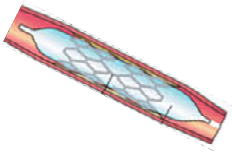


Prevention

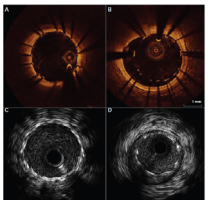
1-Good lesion preparation



2-Post-dilation



3-Using intravascular Imaging



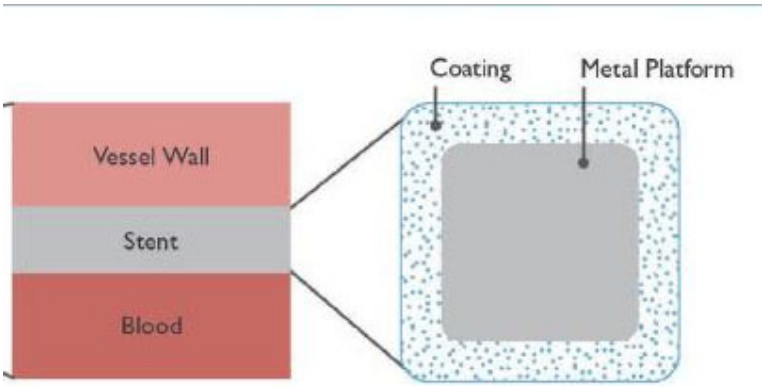
Drug-eluting stents

1- **platform** (e.g., thin-strut cobalt chromium vs. thick-strut stainless steel)

2- **polymer** (thinner and/or biodegradable and/or its absence)

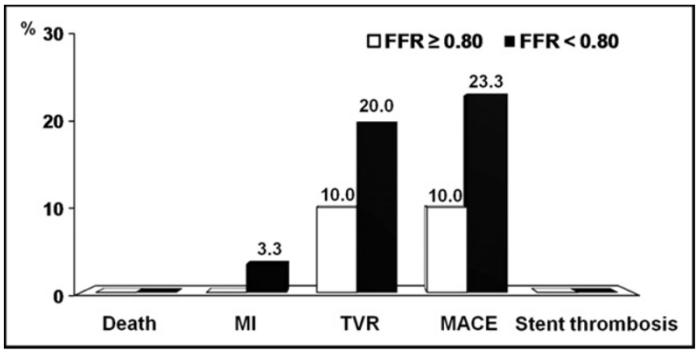
3- **drug** (biolimus and zotarolimus).

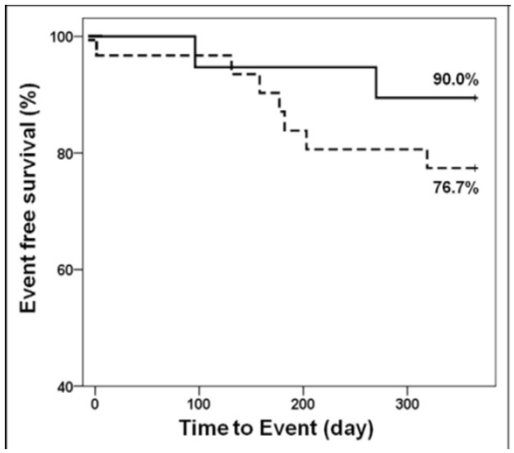
TLF in newer generation stent is about 5% first year, 12% over 5 years



Lee 2014, AJC
Brener 2013, AHJ
Harjai 2013
Kedhi 2010
Madhavan 2020 JACC

What about treatment?
FFR cut-off 0.80 is validated to guide treatment





Nam 2011, AJC

Guidelines for Treatment of ISR

Balloon angioplasty, BMS, DES

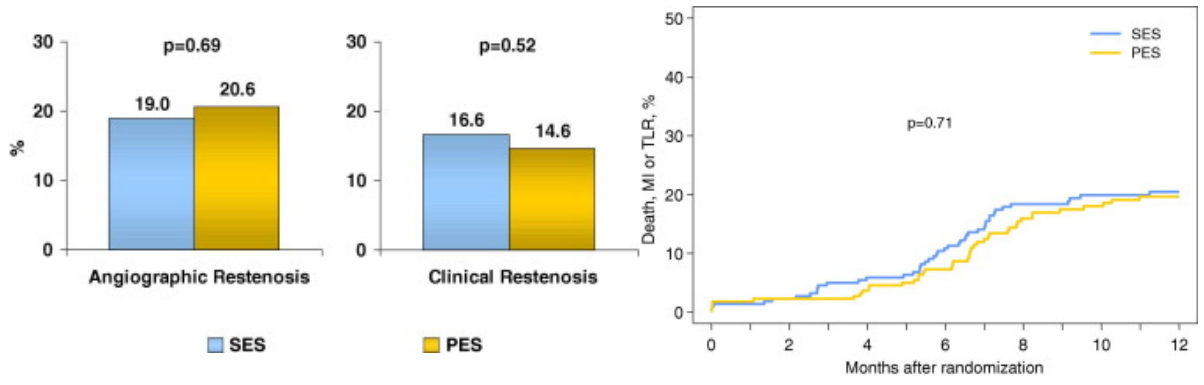
DES , DCB

Guidelines recommendations mostly apply to the treatment for first episode of ISR

Treatment of DES ISR is not clear like BMS ISR (Drug failed one already)

ISAR-DESIRE 2
DES for SES-ISR

450 patients
Clinical follow-up at one year



Garg et al. 2007 CCI

116 patients

TABLE IV. Twelve-Month Major Cardiac Adverse Event Rate

	Different DES	Same DES	*P* Value
Number of patients	43	40	
Q-wave myocardial infarction	0	3 (7.7%)	0.240
Death	3 (7.5%)	1 (2.7%)	0.616
TVR	11 (26.8%)	12 (30.8%)	0.697
TLR	6 (15.0%)	7 (17.9%)	0.724
MACE-TVR	14 (32.6%)	14 (35.0%)	0.814
MACE-TLR	9 (21.4%)	9 (22.5%)	0.907
Stent thrombosis	0	1 (2.5%)	0.482

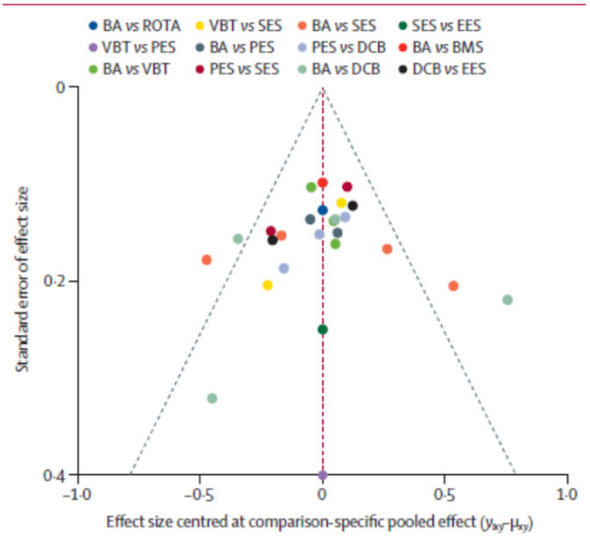
TVR, target vessel revascularization; TLR, target lesion revascularization; MACE, major adverse cardiac events.

Siontis 2015, Lancet
Largest network meta-analysis to date

First line
DES (EES)
DCB

BA, VBT, ROTA, and BMS are inferior

The study did not include resistant ISR



Resistant (recurrent) in-stent restenosis

Recurrent (resistant) ISR

1-more than one episode of ISR.

2-last layer of stenting is DES.

Table. Waksman In-Stent Restenosis Classification

Type	Definition		Treatment Options
I	Mechanical	Underexpansion (Type I A)	High-pressure balloon
		Stent fracture (Type I B)	DES
II	Biologic	Intimal hyperplasia (Type II A)	Balloon, DCB, DES, and VBT
		Neoatherosclerosis, noncalcified (Type II B)	DCB and DES
		Neoatherosclerosis, calcified (Type II C)	Scoring balloon, ELCA, and RA
III	Mixed pattern: Combined mechanical and biologic etiology		High-pressure balloon with DCB, DES, or VBT
IV	Chronic total occlusion		DCB or DES, VBT for multiple layers, CABG as needed
V	>2 layers of stent		Balloon, DCB, VBT, and CABG

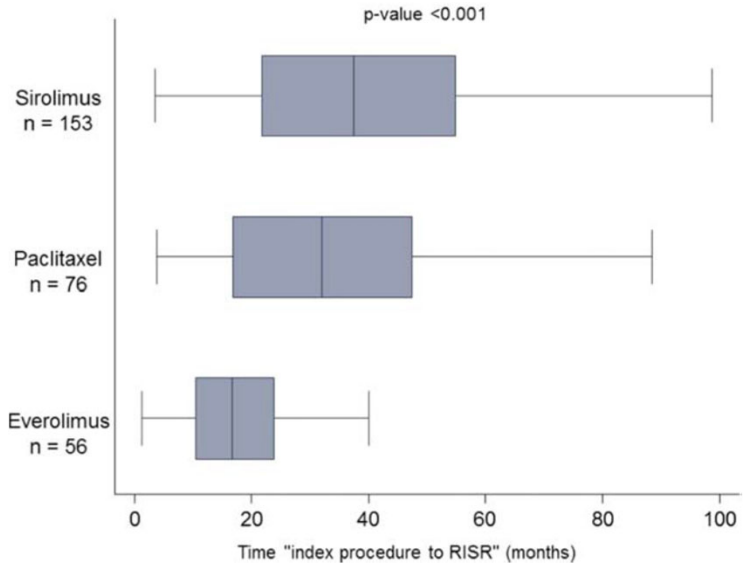
CABG indicates coronary artery bypass graft; DCB, drug-coated balloon; DES, drug-eluting stent; ELCA, excimer laser coronary atherectomy; RA, rotational atherectomy; and VBT, vascular brachytherapy.

Waksman 2019 Circ Int.

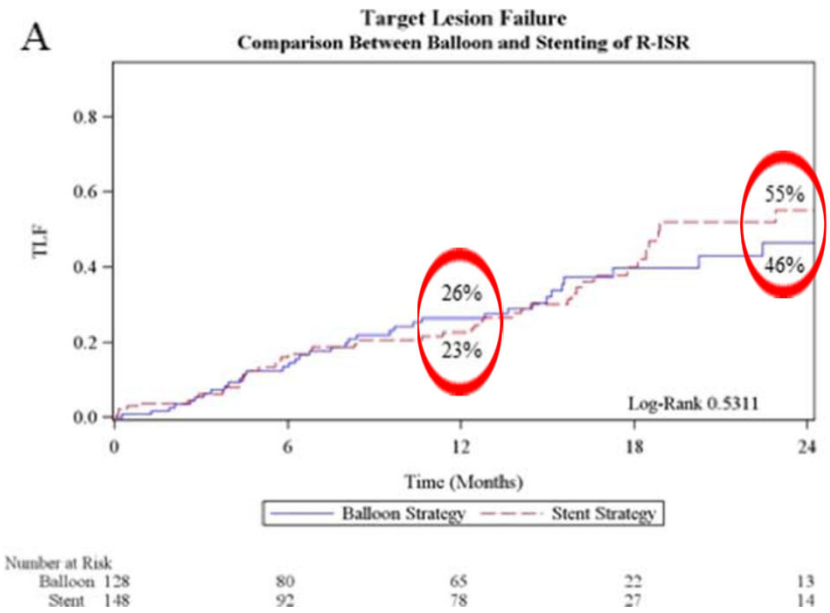
Theodoropoulos et al. 2016, CCI

19,992 patients (PCI with DES)

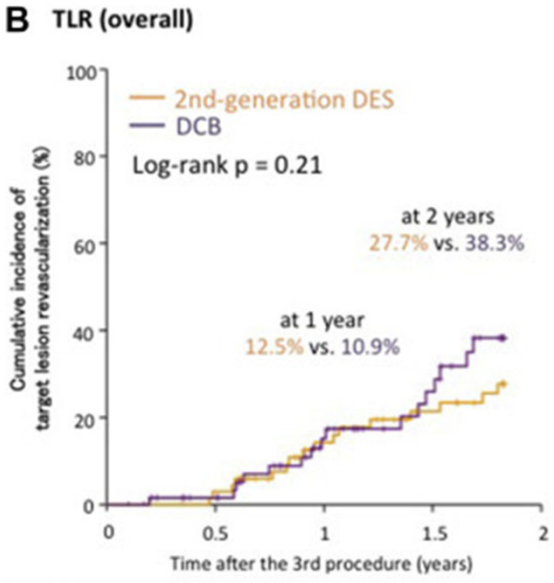
10.8% ISR
1.4% resistant ISR



Theodoropoulos 2016, CCI

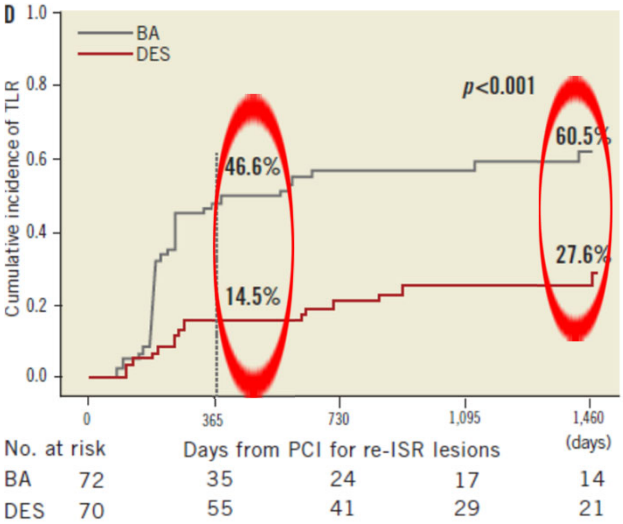


Kawamoto et al. 2015, JACC INT (171 lesions with resistant ISR)

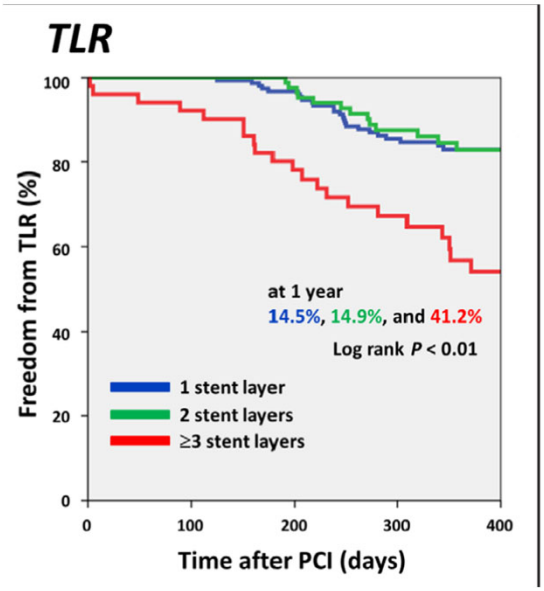


Kubo et al. 2013 EuroIntervention

142 patients with resistant ISR (2 layers)- **4 years**
Compared BA vs. DES



Yabushita et al. 2018, Circ Int. (304 patients)



Conclusion of these numbers?

1-highly complex lesions

2- high incidence TLR
27% in 2 years (the least complex subset)

41% in one year (the most complex subset with 3 layers of stents).

Why does it happen?

1- More **metal layers-**→ more difficult to expand

2- **Inflammatory** responses to drugs/polymers/struts

3-Drug resistance

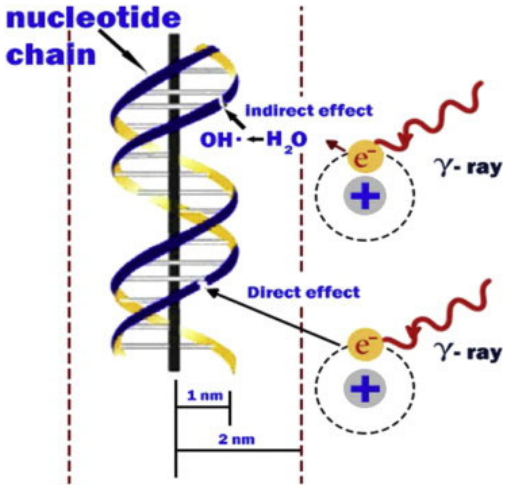
Ferri. 2017 CCI

Intracoronary vascular brachytherapy (VBT)

Ionizing radiation

1-Reduces neointimal growth
a-reduces vascular smooth muscle proliferation
b-reduces adventitial fibrosis and vessel remodeling
c-Interrupting the cell cycle and causing apoptosis

2-Reduces inflammation
a-reduces leukocyte chemotaxis and cytokine induction
b-reduces matrix secretion by macrophages
c-reduces proinflammatory cells

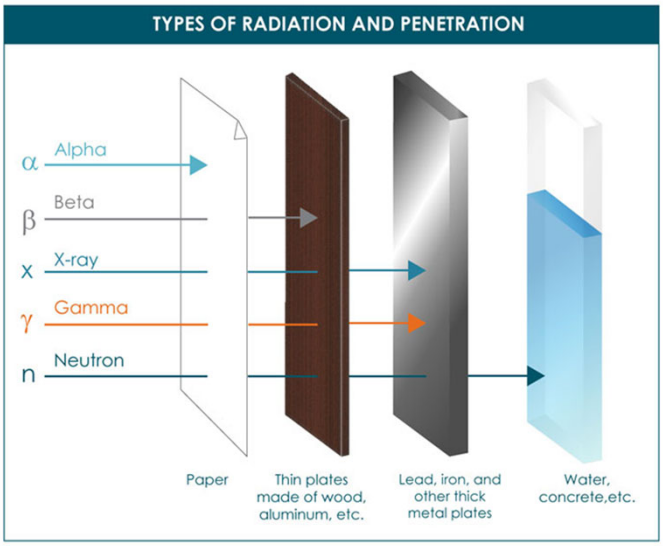


Waksman 1997 Circulation
Kuchulakanti 2005 CRM

Intravascular radiation

Gamma (Iridium Ir 192)

Beta (stronium-90/yttrium-90 isotope)

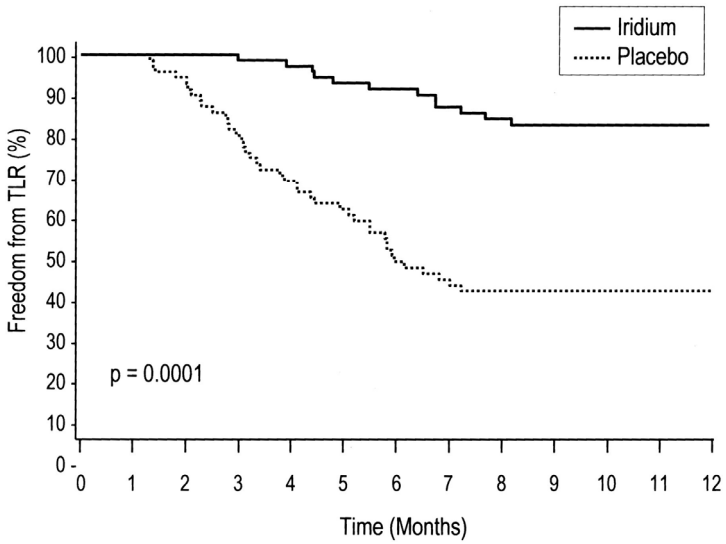


Human studies

Safety
Single arm studies
Silber 2000. Z Kardiolo
Coen 2000 Cardio. Rad. Med.

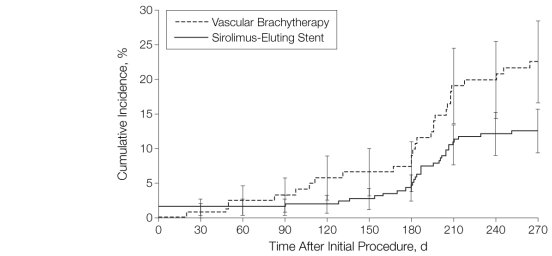
RCTs (BMS ISR)
Waksman 2000 Circulation (15 Gy)
Leon 2001 NEJM

Approval for BMS ISR



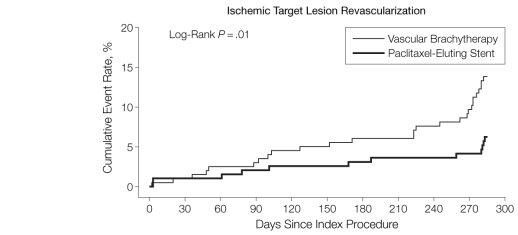
Drug-eluting stents were superior in BMS ISR

Holmes 2006 JAMA
Stone 2006 JAMA



No. at Risk

Sirolimus-Eluting Stent	259	255	255	255	254	252	250	245	227	222
Vascular Brachytherapy	125	125	123	119	118	115	114	111	94	92



No. at Risk

Vascular Brachytherapy	201	200	197	194	192	188	186	182	182	179
Paclitaxel-Eluting Stent	195	195	192	192	190	188	186	185	184	184

Death of the phoenix

VBT in DES ISR

- **Torguson 2006, AJC (VBT vs. DES)**

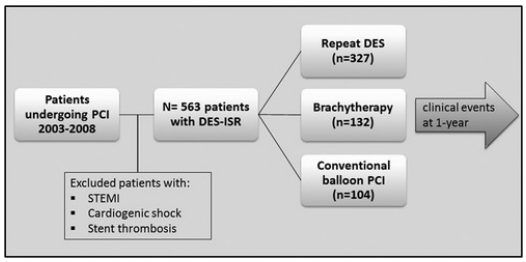
TLR was similar between both at 8 months (10% vs 18%, p was nonsignificant)

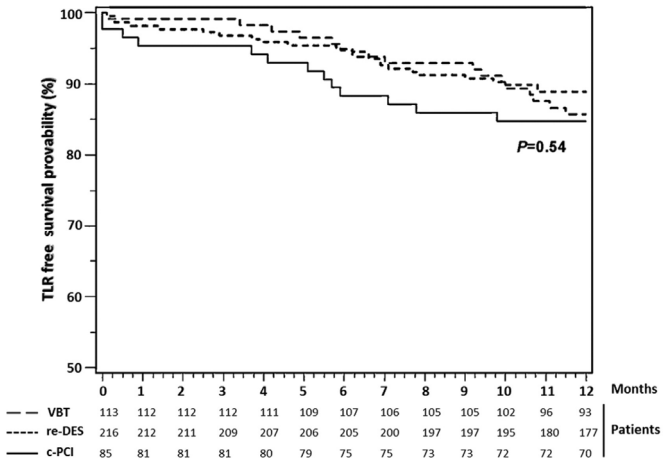
- **Bonello 2008, J Int Card**

TLR 11% at one year

Maluenda et al. 2012, Circ Interventions (VBT vs. DES)

10.3% re-DES, 14.1% (VBT), 14.6% (balloon)





Resistant DES-ISR

Re-DES is challenging and unlikely to be successful

VBT

- No additional layers of metal or polymers
- No encroachment on an already narrowed lumen
- less inflammation
- Avoid drug resistance

Negi et al. 2016 JACC

Medstar, Washington
186 patients (283 lesions) (2004-2012)

Number of previous ISR episodes	
1-2	4
3-4	63
>4	25
Unknown	8
Previous DES information	
First generation	64
Second generation	36

	30 Days	6 Months	1 Year	2 Years	3 Years
TLR	1 (0.5)	6 (3.3)	22 (12.1)	31 (17.2)	30 (19.4)
Surgical TLR	0	0	0	3 (1.6)	5 (2.8)
TVR	3 (1.6)	13 (7.1)	35 (19.1)	54 (30)	55 (30.5)
Surgical TVR	0	0	0	3 (1.6)	5 (2.8)
MI	0	1 (0.5)	3 (1.5)	10 (5.6)	11 (6.7)
LST	0	0	1 (0.5)	1 (0.5)	1 (0.5)
Death	1 (0.5)	7 (3.8)	10 (5.4)	18 (9.8)	23 (13.2)

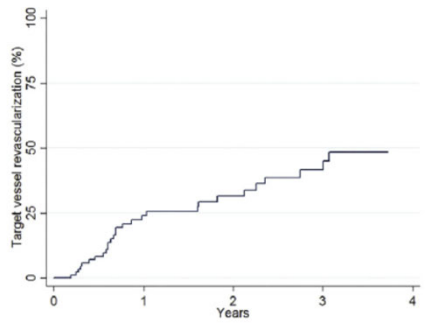
Mangione et al. 2017 AJC

Brigham and Women's hospital, Boston
101 patients (101 lesions) (2009-2015)

Previous stent layers	2 (2 - 3)
1	1 (1%)
2	60 (60%)
3	29 (28%)
4	8 (8%)
5	3 (3%)
Prior drug eluting stent	101 (100%)
1st generation only	5 (5%)
2nd generation only	19 (19%)
1st and 2nd generation	16 (16%)
Unknown	61 (60%)

Variable	Event rates at 1 year	Event rates at 2 years	Event rates at 3 years
Target vessel revascularization	24%	32%	42%
Non-fatal myocardial infarction	0%	3.5%	6%
Non-target vessel revascularization	12%	14%	22%
Death	8.5%	12%	16%

A



Mangione et al. 2017 AJC

Restenosis pattern	
Focal	35 (35%)
Diffuse	54 (53%)
Proliferative	12 (12%)

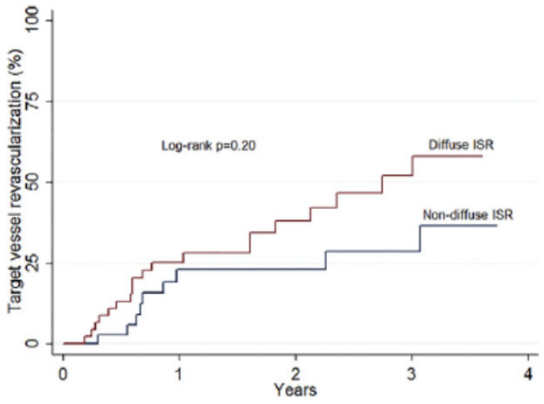


Table 4
Adjusted model for target vessel revascularization

	HR	95% CI	p Value
Female sex	2.37	1.02 – 5.52	**0.04**
Previous stroke/transient ischemic attack	2.40	0.55 – 10.48	0.24
Previous myocardial infarction	0.49	0.20 – 1.20	0.17
Left internal mammary artery treated	3.95	0.88 – 17.90	0.07
Diffuse in-stent restenosis	2.95	1.21 – 7.17	**0.01**
Hypertension	0.14	0.02 – 1.35	0.09

$p < 0.05$ are indicated in bold.

Meraj at al. 2020 CCI

Northwell Hospital, NY
290 patients (290 lesions) (2011-2016)

Number of previous ISR procedures[a]	
1	160 (61.33%)
2	70 (26.8%)
3	24 (9.2%)
4	3 (1.1%)
5	3 (1.1%)
6	1 (0.4%)

Events on follow up	1-year(*n* = 290)	2-year (*n* = 285)
Instent restenosis	36 (12.4%)	42 (14.7%)
Stroke[a]	1 (0.3%)	1 (0.3%)
All-cause mortality	5 (1.7%)	6 (2.1%)
Myocardial infarction	10 (3.4%)	11 (3.9%)

Varghese et al. 2018 Circ Int.

Mount Sinai, NY
Only study to have a control arm
Resistant ISR with at least 2 layers of stents (2011-2015)

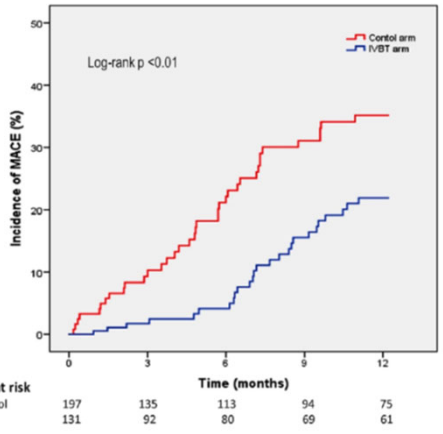
197 patients/lesions in VBT group/131 in control group

Propensity matched analysis (91 patients/lesions in each group)

No. of prior procedures of same lesion			
2–3	51 (26)	49 (37)	0.249
4–5	104 (53)	74 (56)	0.074
>5	6 (3)	1 (1)	0.168
Unknown	36 (18)	7 (5)	0.415
No. of stent layers			
2	147 (75)	111 (85)	0.253
3	47 (24)	17 (13)	0.285
>3	3 (2)	3 (2)	0.059
Last stent diameter*	3.0±0.4	3.0±0.4	0.143
Last stent length*	22.7±7.5	21.8±6.7	0.127
Last DES generation*			
First gen	23 (14)	19 (15)	0.030
Second gen	148 (86)	112 (85)	0.030
Time since last DES restenosis, d	465±367	508±310	0.127

Varghese 2018 Circ Int.

	Total Study Population			Propensity-Matched Cohort			
Variable	IVBT (n=197)	Control (n=131)	*P* Value	IVBT (n=91)	Control (n=91)	Hazard Ratio (95% CI)	*P* Value
TLR	21 (10.7)	29 (22.1)	0.07	11(12.1)	22 (24.2)	0.48 (0.23–1.00)	0.05
TVR	30 (15.2)	30 (22.9)	0.33	16 (17.6)	23 (25.3)	0.69 (0.36–1.33)	0.27
MI	6 (3.0)	9 (6.9)	0.13	1 (1.1)	6 (6.6)	0.14 (0.02–1.22)	0.08
ST	2 (1.0)	2 (1.5)	0.93	1 (1.1)	1 (1.1)	1.16 (0.07–19.07)	0.92
Death	2 (1.0)	6 (4.6)	0.09	1 (1.1)	4 (4.4)	0.14 (0.01–1.53)	0.14
MI/death	8 (4.1)	12 (9.2)	0.10	2 (2.2)	8 (8.8)	0.16 (0.03–0.86)	0.03
TVR/MI/death	35 (17.8)	38 (29.0)	0.09	17 (18.7)	29 (31.9)	0.51 (0.27–0.94)	0.03
MACE	26 (13.2)	37 (28.2)	0.01	12 (13.2)	28 (30.8)	0.37 (0.18–0.73)	<0.01

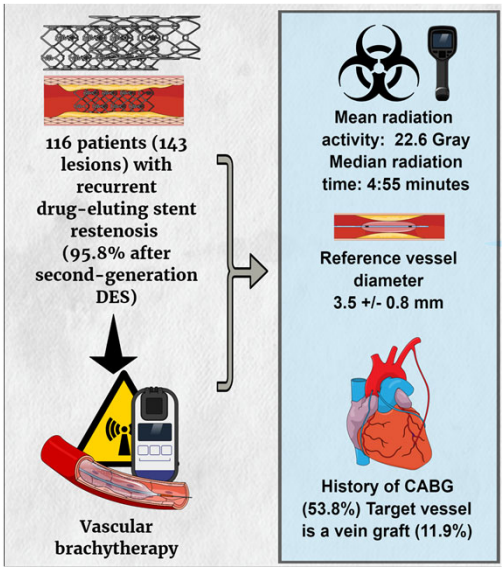


Our results

Outcomes of intravascular brachytherapy for recurrent drug-eluting in-stent restenosis

Michael Megaly MD, MS[1,2] | Matthew Glogoza MD[1] | Iosif Xenogiannis MD[1] |
Evangelia Vemmou MD[1] | Ilias Nikolakopoulos MD[1] | Laura Willson MD[3] |
David J. Monyak MD[3] | Patsa Sullivan MD[3] | Larissa Stanberry PhD[1] |
Paul Sorajja MD[1] | Ivan Chavez MD[1] | Michael Mooney MD[1] |
Jay Traverse MD[1] | Yale Wang MD[1] | Santiago Garcia MD[1] |
Anil Poulose MD[1] | Martin Nicholas Burke MD[1] | Emmanouil S. Brilakis MD, PhD[1]

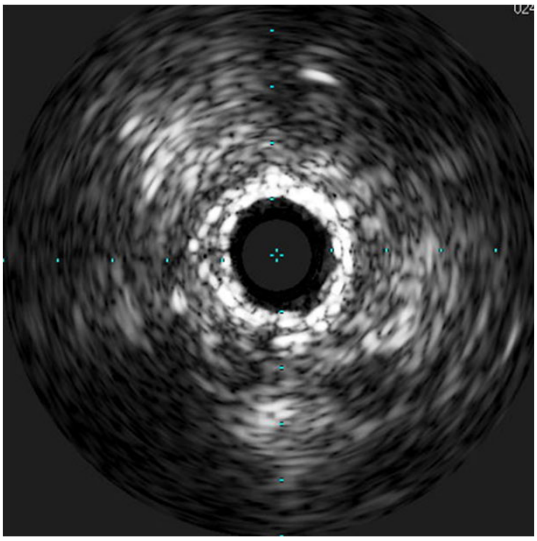
2014-2018



Clinical presentation	
Stable angina	67 (46.9%)
Cardiomyopathy	3 (2.1%)
Unstable angina	47 (32.9%)
NSTEMI	25 (17.5%)
STEMI	1 (0.7%)

Restenosis pattern on the initial angiogram	
Focal	52 (36.4%)
Diffuse	71 (49.7%)
Proliferative	5 (3.5%)
Chronic total occlusion	12 (8.4%)

Last DES type	
Second-generation	137 (95.8%)
Unknown	6 (4.2%)
Previous stent layers	
1	24 (16.8%)
2	66 (46.2%)
3 or more	53 (37%)
Total ISR episodes	
2	16 (11.2%)
3	60 (42%)
4 or more	67 (46.9%)



IVUS use (29%)

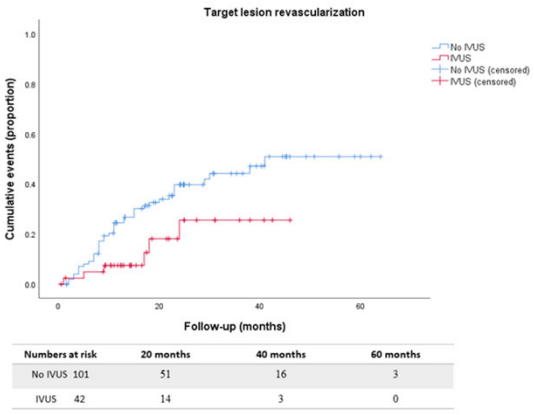
		Kaplan Meier estimates		
	N = 143	1 year	2 years	3 years
Target lesion revascularization	46 (32.2%)	27 (18.9%)	42 (29.4%)	44 (30.8%)
Target lesion revascularization (PCI)	43 (30%)	25 (17.5%)	40 (27.9%)	42 (29.4%)
Target lesion revascularization (surgical)	3 (2.1%)	2 (1.4%)	2 (1.4%)	2 (1.4%)
Redo brachytherapy	4 (2.8%)	3 (2.1%)	4 (2.8%)	4 (2.8%)
Target lesion myocardial infarction	16 (11.2%)	8 (5.6%)	15 (10.5%)	15 (10.5%)
Stent thrombosis	3 (2.1%)	3 (2.1%)	3 (2.1%)	3 (2.1%)
Target lesion unstable angina	27 (18.9%)	15 (10.5%)	23 (16.1%)	23 (16.1%)
Target lesion cardiac death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Target lesion failure	51 (35.7%)	30 (20.1%)	47 (32.9%)	49 (34.3%)

A little reminder

1-highly complex lesions

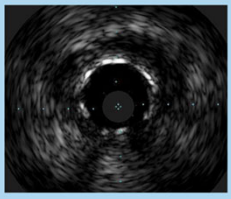
2- high incidence TLR
27% in 2 years (the least complex subset)

41% in one year (the most complex subset with 3 layers of stents).



Numbers at risk	20 months	40 months	60 months
No IVUS 101	51	16	3
IVUS 42	14	3	0

Log rank p=0.038



Using IVUS was associated with lower risk of target lesion revascularization 14.3% vs. 39.6% (log-rank p= 0.038)

Independent predictors of Target lesion failure

Initial presentation with acute coronary syndrome (HR 2.04 (95% CI 1.16-3.59), p=0.019

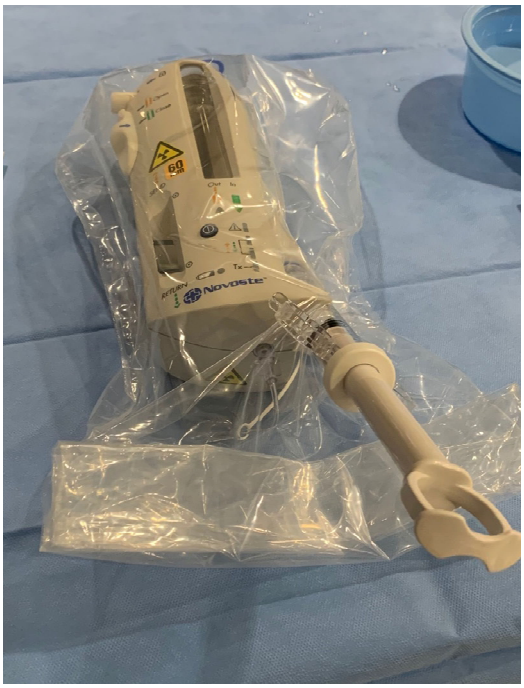
The procedure

Novoste Beta-Cath 3.5F System

Beta radiation
stronium-90/yttrium-90 isotope
(less penetration- safer)

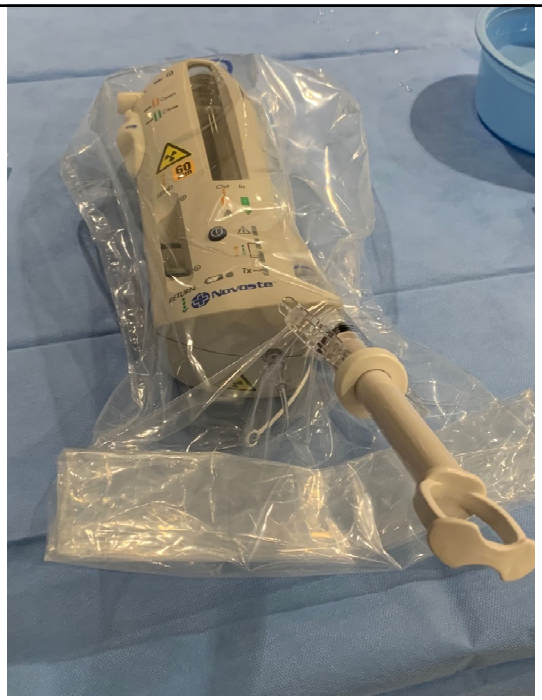
Energies up to 2.27 Mev
Radioactive half-life of 28.8 years.

Source lengths of 40 and 60 mm

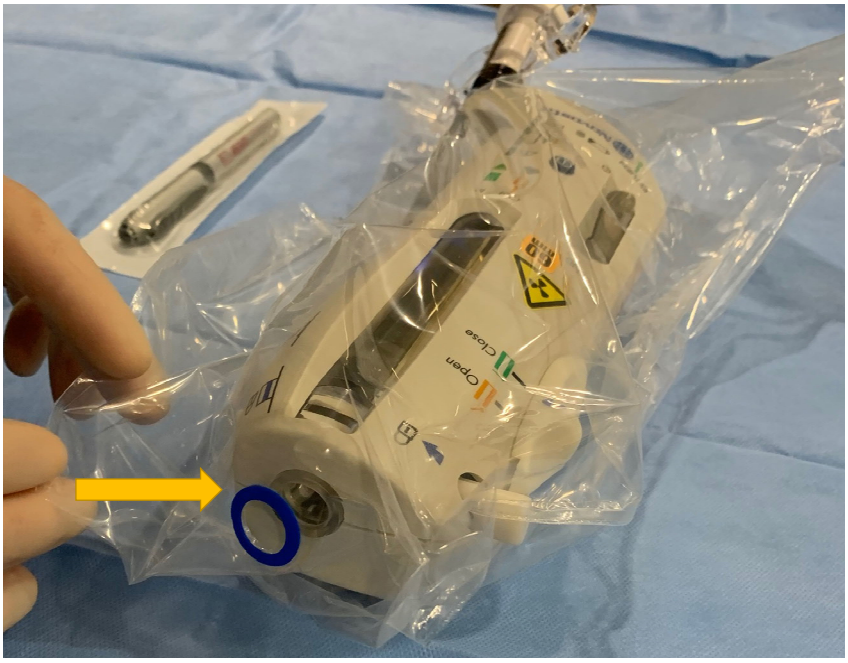


Amount of radiation delivered
18.4 or 23 Gy at a depth of 2 mm from the center of the source

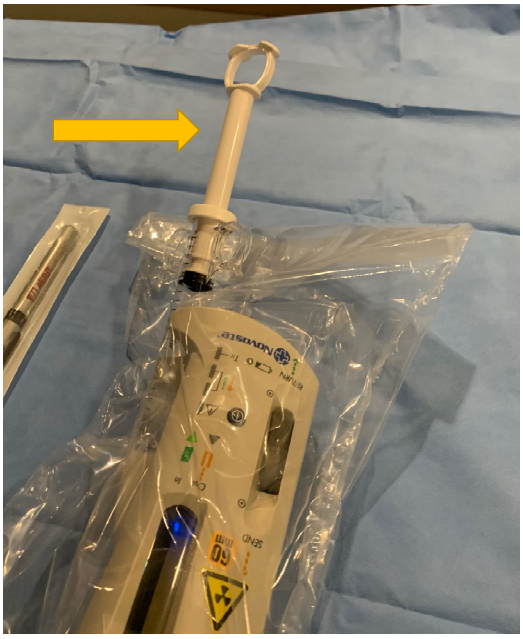
Dwell (treatment time)
Up to 5 minutes
determined by both the source length and vessel diameter.

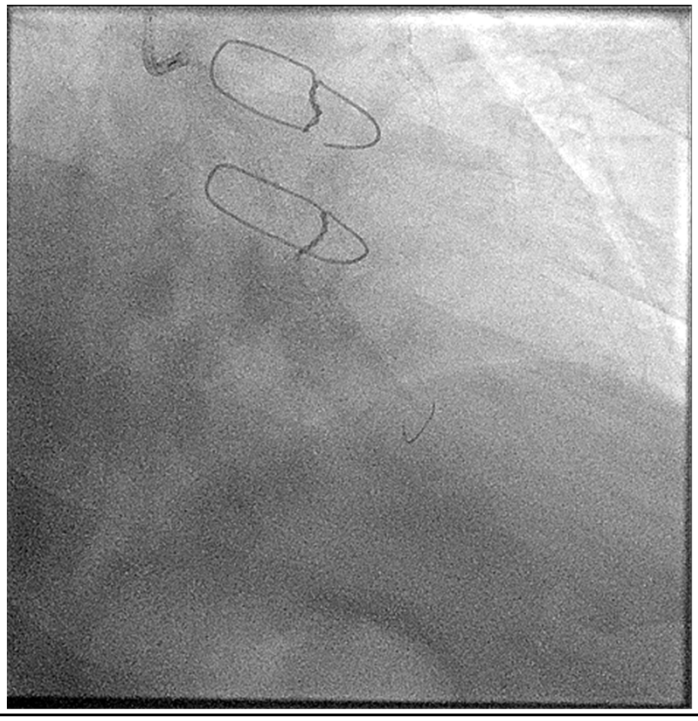


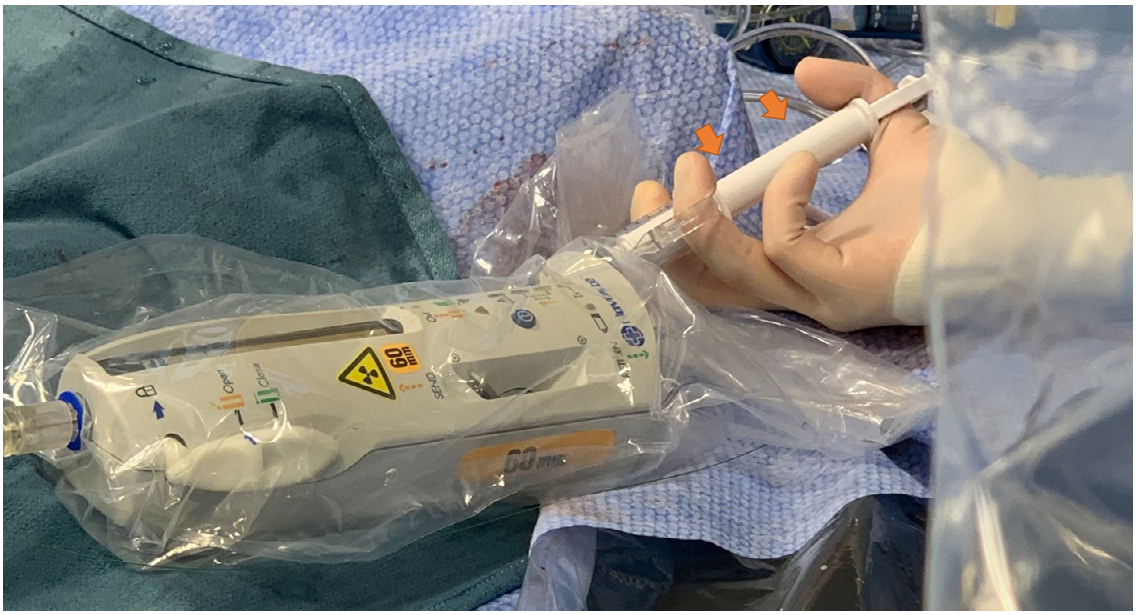
Connect to the catheter

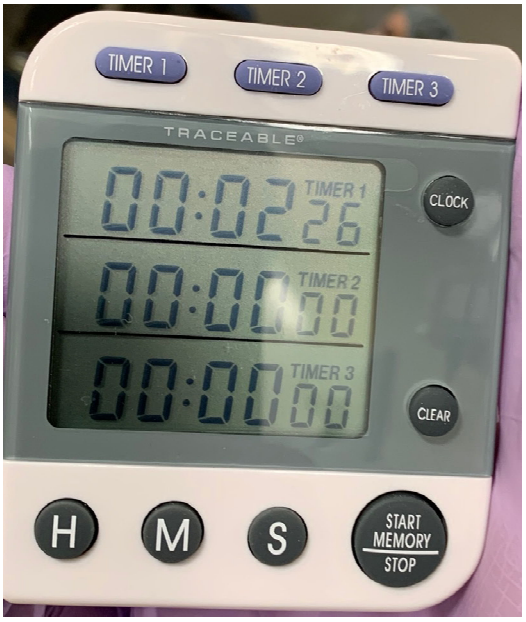


Active seeds are pushed in and then back through a train by hydraulic pressure








TIMER 1
TIMER 2
TIMER 3
TRACEABLE
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TIMER 1
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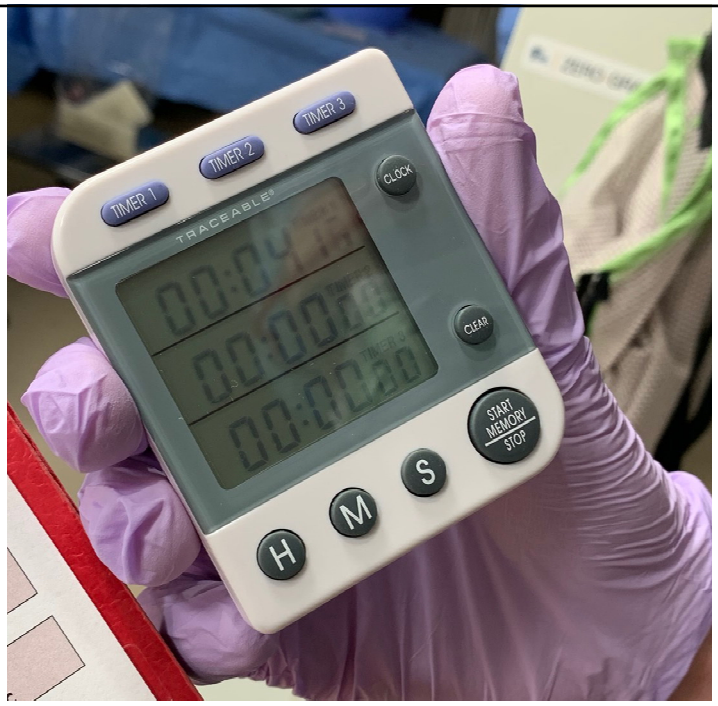
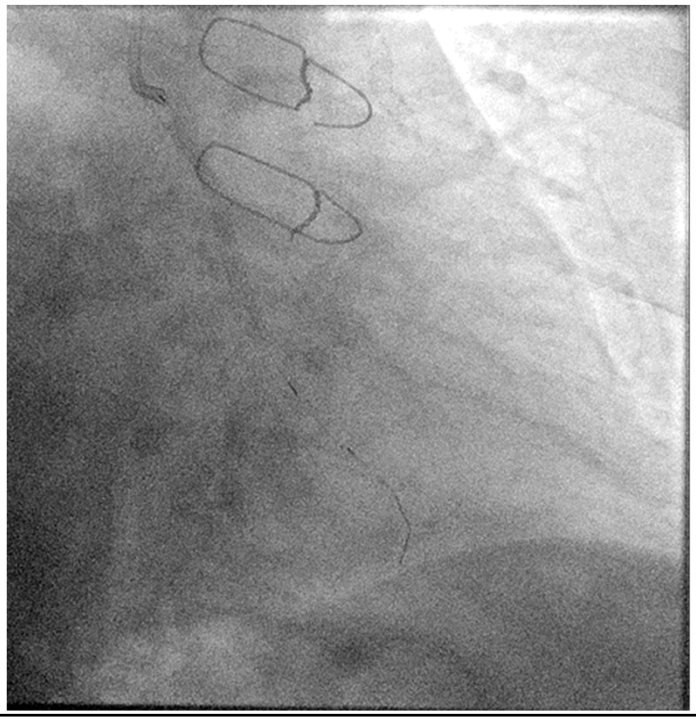
TIMER 2
00:00 00
TIMER 3
CLOCK
CLEAR
H
M
S
START
MEMORY
STOP



Seed retraction



Survey at the end

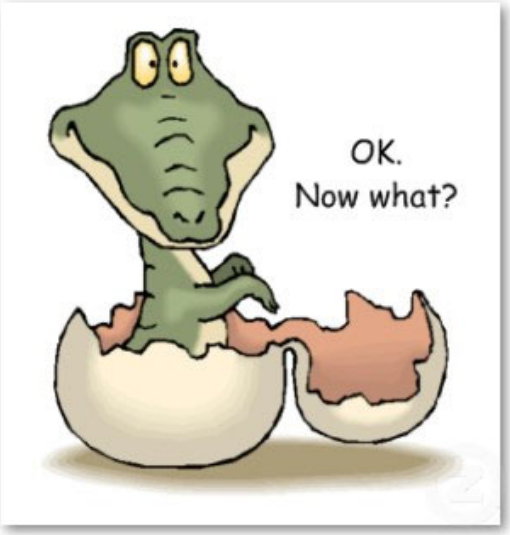
VBT concerns and are they addressed currently

1-Edge restenosis (geographic mismatch)
Radiating proximal and distal to the lesion

2- Late stent thrombosis especially with concurrent stent placement.
No stenting, Newer antiplatelet agents

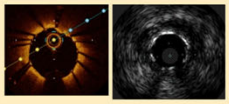
3-Late catch up phenomenon between 6 and 60 months

Stone 2006 JAMA
Holmes 2006 JAMA
Waksman 2004 Circulation



Proposed approach to drug-eluting stent in-stent restenosis

First restenosis event



Intravascular imaging (OCT or IVUS)

Mechanical factors

Stent underexpansion
Stent malapposition

1-Full expansion and apposition of the stent
2-Second-generation DES, DCB, or consideration of CABG (according to patient preference)

Stent fracture

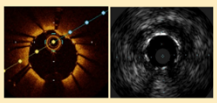
Second-generation DES or consideration of CABG according to patient preference

No mechanical factors

1-Confirm compliance with medications and control other comorbidities (e.g., DM)
2- Second-generation DES, DCB, or consideration of CABG according to patient preference

Megaly 2020 CCI

Recurrent restenosis



Intravascular imaging (OCT or IVUS)

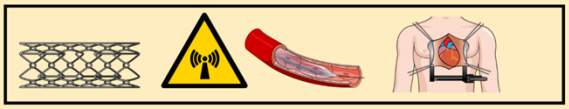
Mechanical factors

Stent underexpansion
Stent malapposition

1-Full expansion and apposition of the stent
2-Second-generation DES
3-DCB (only for second restenosis event)
4-Consider VBT
5- Consider CABG

Stent fracture

1-second-generation DES
2-Consider VBT
3-Consider CABG

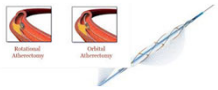


No mechanical factors

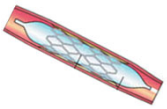
1-Confirm compliance with medications and control other comorbidities (e.g., DM)
2-DCB (only for second restenosis event)
2-Consider VBT with or without stenting with a second-generation DES

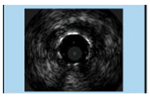
Megaly 2020 CCI

Take home



1.Prevention of ISR is the best treatment.

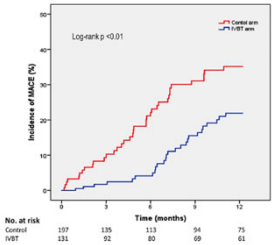




2.First step in evaluation of ISR is intravascular imaging

Using IVUS was associated with lower risk of target lesion revascularization 14.3% vs. 39.6% (log-rank p= 0.038)

3.Vascular brachytherapy for resistant DES ISR
TLR in complex subset of lesions is 30% at 3 years



Thank you

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Cath Ed
By Michael Megaly