CLINICAL POTENTIAL OF LASER WAKEFIELD ACCELERATOR ELECTRON BEAM SOURCES: A THOUGHT EXPERIMENT

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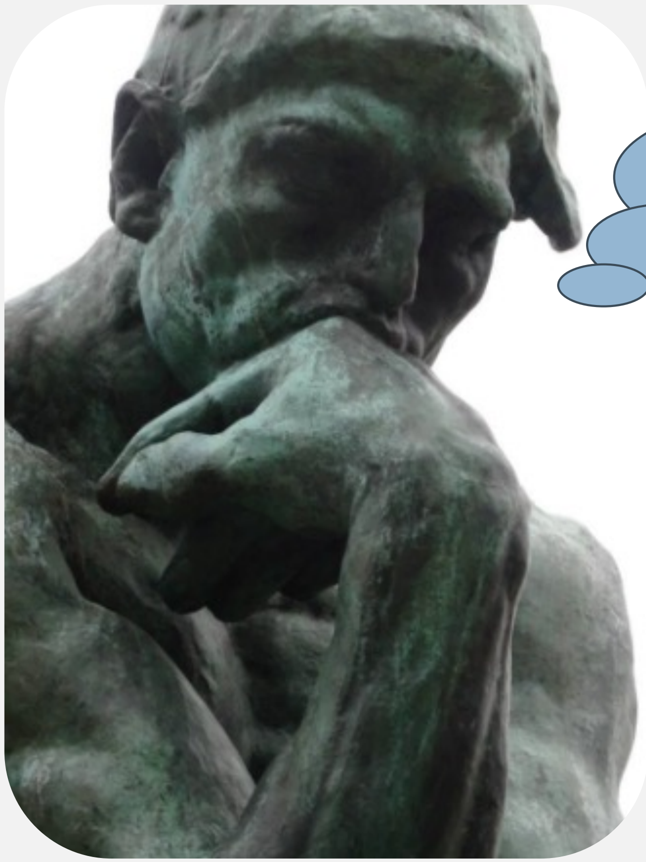
February 7, 2025


I can read
I can think



Possible clinical uses for a novel radiation source


VARIAN
Linear accelerator
PERFEXION
Radionuclide teletherapy
Xoft
Miniature x-ray source
Radiopharmaceutical
Radionuclide brachytherapy

COMPARED TO A LWFA RADIATION SOURCE …

	Linear accelerator or teletherapy unit	Radionuclide brachytherapy	Electronic brachytherapy (intra-op or intravascular)
Device size	Much much larger (req. shielded vault)	Larger (comparable to check in luggage)	Comparable (comparable to carry on luggage or personal item)
Applicator size	Larger (external only)	Larger (3.5 x 0.9 mm seeds)	Comparable (0.38 mm diam)
Portability	Not at all	Not at all	A little
Dose rate	Much lower	Much lower	Much lower
Directional	N	N	N
Pulse control / modulation	N	N	N
Cost (est.)	Much much higher	Higher	Higher
Disciplinary jurisdiction	Radiation oncology	Radiation oncology	Radiation oncology
Regulatory jurisdiction	State	NRC	State

WHAT CAN YOU DO WITH A NOVEL (LWFA) SOURCE?

	Replace existing radiation technology	**Replace other technology**	**New applications**
Indications	Same	Same or new	New
Toxicities	Less	Same or less	TBD
Cost	Same or less	Same or less	TBD
Example(s)	▪ Radionuclide brachytherapy ▪ IOERT ▪ Superficial electron therapy	▪ Cardiac arrythmia ablation ▪ Radiofrequency ablation	▪ TBD

photonics

MDPI

Perspective

Fiber-Optic Based Laser Wakefield Accelerated Electron Beams and Potential Applications in Radiotherapy Cancer Treatments

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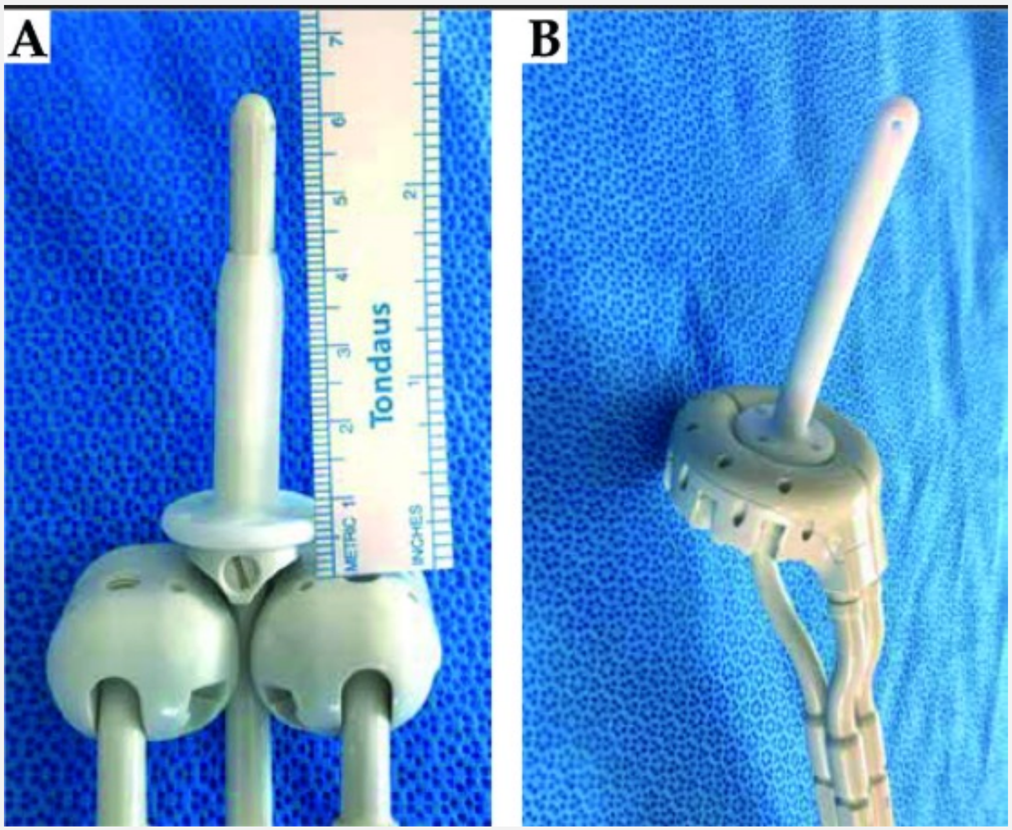
Abstract: Ultra-compact electron beam technology based on laser wakefield acceleration (LWFA) could have a significant impact on radiotherapy treatments. Recent developments in LWFA high-density regime (HD-LWFA) and low-intensity fiber optically transmitted laser beams could allow for cancer treatments with electron beams from a miniature electronic source. Moreover, an electron beam emitted from a tip of a fiber optic channel could lead to new endoscopy-based radiotherapy, which is not currently available. Low-energy (10 keV–1 MeV) LWFA electron beams can be produced by irradiating high-density nano-materials with a low-intensity laser in the range of ~10^{14} W/cm^2. This energy range could be useful in radiotherapy and, specifically, brachytherapy for treating superficial, interstitial, intravascular, and intracavitary tumors. Furthermore, it could unveil the next generation of high-dose-rate brachytherapy systems that are not dependent on radioactive sources, do not require specially designed radiation-shielded rooms for treatment, could be portable, could provide a selection of treatment energies, and would significantly reduce operating costs to a radiation oncology clinic.

Keywords: LWFA; fiber optics; medicine; brachytherapy; cancer

check for updates

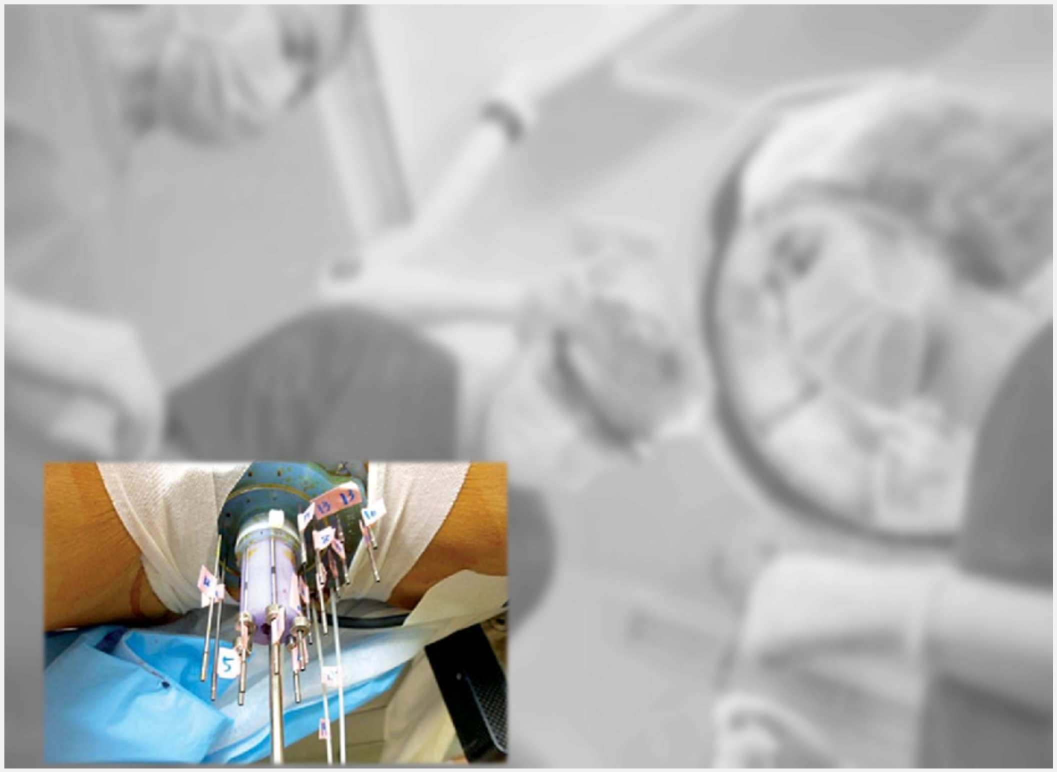
Citation: Roa, D.; Kuo, J.; Moyses, H.; Taborek, P.; Tajima, T.; Mourou, G.; Tamanoi, F. Fiber-Optic Based Laser Wakefield Accelerated Electron Beams and Potential Applications in Radiotherapy Cancer Treatments. *Photonics* **2022**, 9, 403. https://doi.org/10.3390/photonics9060403



Mehta S, et al. J Contemp Brachytherapy, 2019.

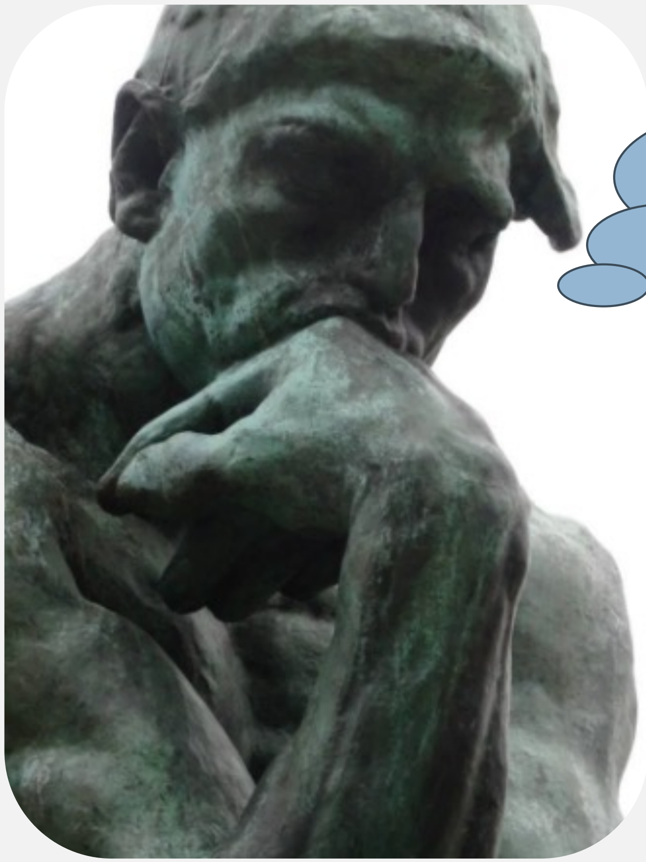
	LWFA	^{192}IR	^{60}Co	Electronic
Capital cost (est.)	$100-300K	$200-350K	$300K	
Room shielding	None	$200-500K	$300-500K	None
Source replacement	None	$10K q4-6 mo	$130K q60 mo	None
5-yr estimated total	$300K	$910K	$930K	
Main indications	TBD	Gyn brachytherapy	Gyn brachytherapy	Breast brachytherapy

Adapted from Roa, et al. Photonics, 2022



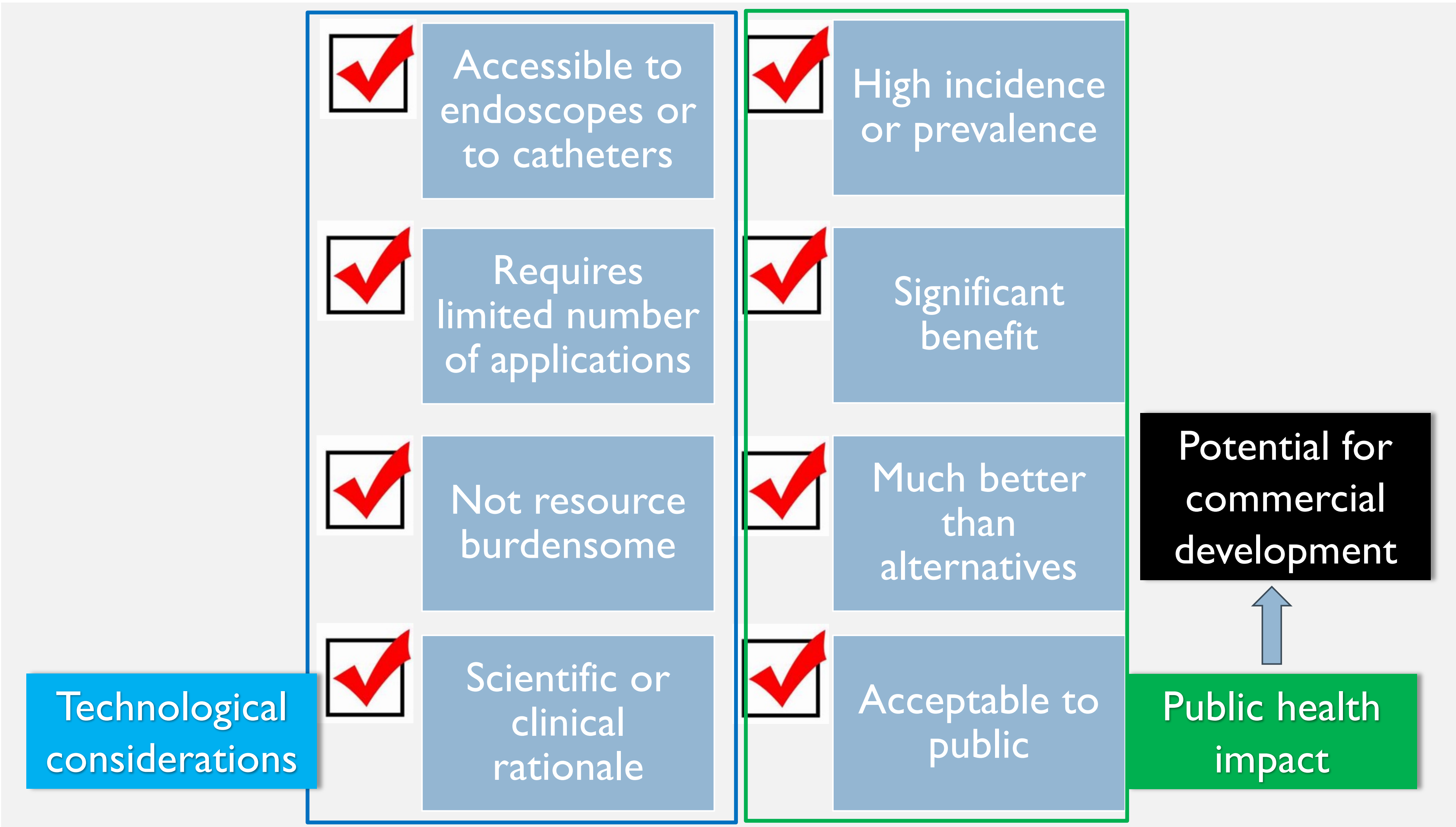
Murakami, et al. J Contemp Brachytherapy, 2016

Hypothetical LWFA HDR

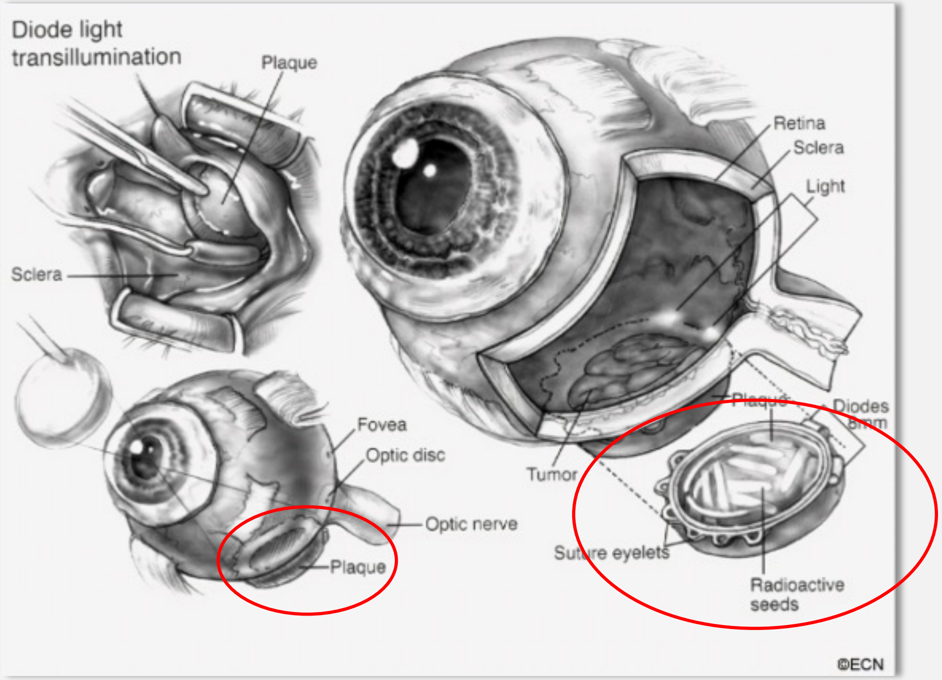


Possible clinical uses for a novel radiation source

everything is something else worth treating


Accessible to endoscopes or to catheters
Requires limited number of applications
Not resource burdensome
Scientific or clinical rationale
Technological considerations
High incidence or prevalence
Significant benefit
Much better than alternatives
Acceptable to public
Public health impact
Potential for commercial development

✔ Accessible to endoscopes or to catheters	✘ High incidence or prevalence
✔ Requires limited number of applications	✔ Significant benefit
✘ Not resource burdensome	✔ Much better than alternatives
✔ Scientific or clinical rationale	✔ Acceptable to public



Niche technology

✓ Accessible to endoscopes or to catheters	✓ High incidence or prevalence
✓ Requires limited number of applications	✓ Significant benefit
✗ Not resource burdensome	± Much better than alternatives
✓ Scientific or clinical rationale	✓ Acceptable to public

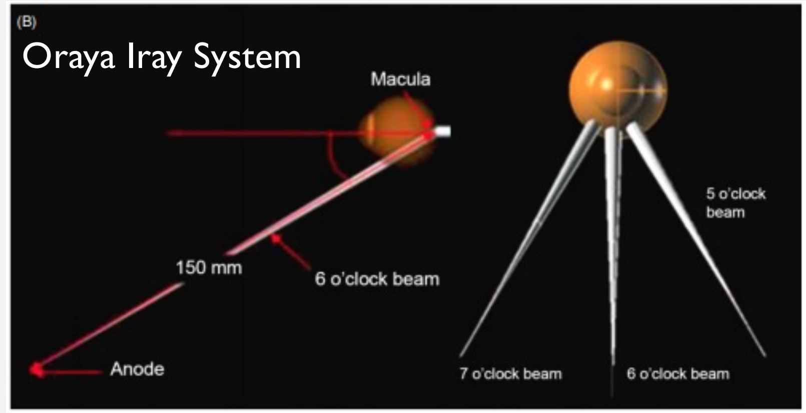
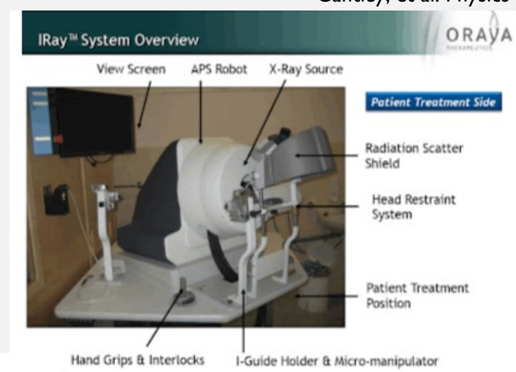


Figure 1. Schematic of eye and treatment geometry. Top: geometric description of the stylized MCNPX eye model employed in this study. Bottom left: sagittal view with the 6 O'clock beam in isolation. Bottom right: frontal view with all three treatment beams.

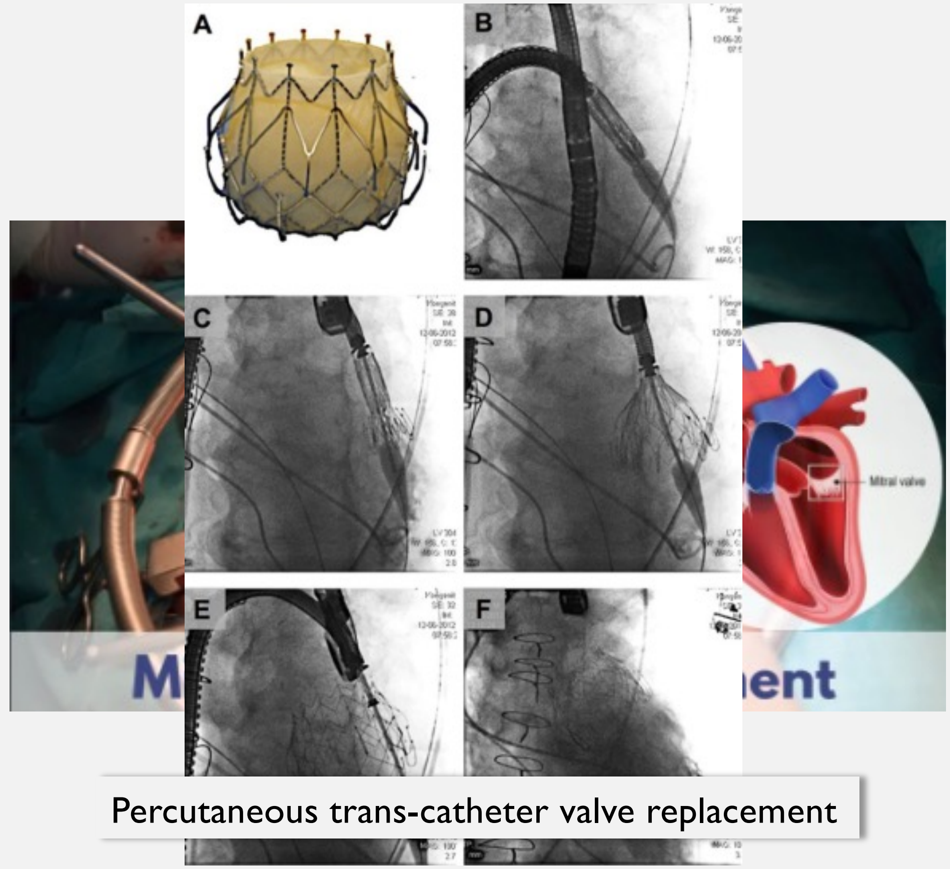
Cantley, et al. Physics Med Biol, 2013



Overlooked technology

- Accessible to endoscopes or to catheters
- Requires limited number of applications
- Not resource burdensome
- Scientific or clinical rationale

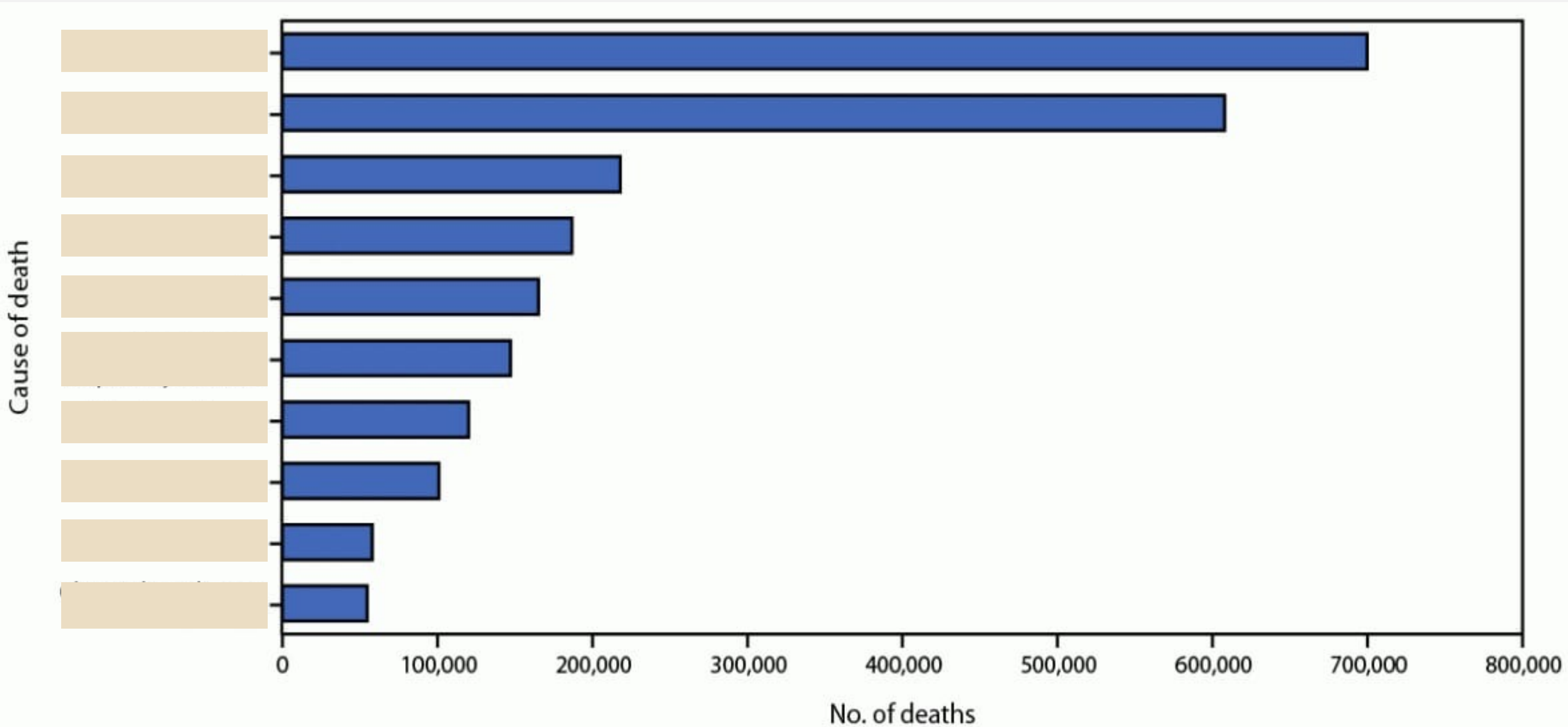
- High incidence or prevalence
- Significant benefit
- Much better than alternatives
- Acceptable to public



Percutaneous trans-catheter valve replacement

Treatment of choice

Leading causes of mortality in the U.S. (2022)



Provisional Mortality Data – U.S., 2022
MMWR

Accessible to endoscopes or to catheters

Requires limited number of applications

Not resource burdensome

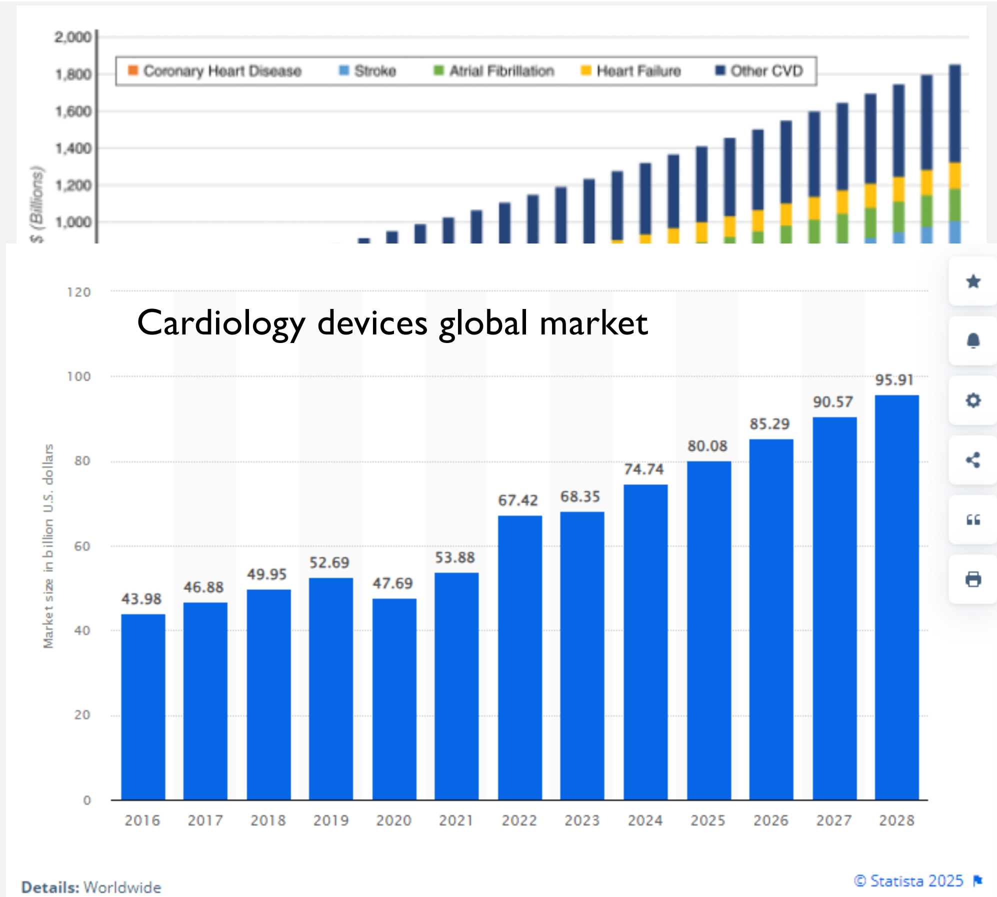
Scientific or clinical rationale

High incidence or prevalence

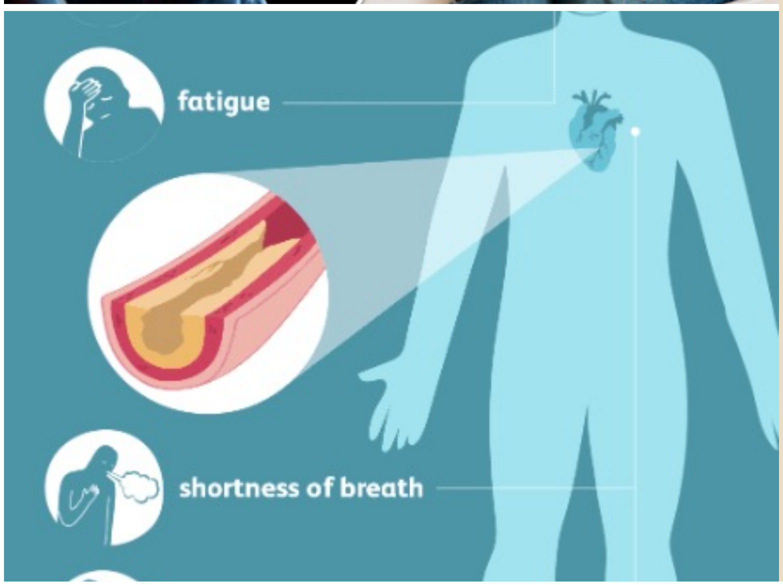
Significant benefit

Much better than alternatives

Acceptable to public



Potential opportunities



CORONARY ARTERY DISEASE

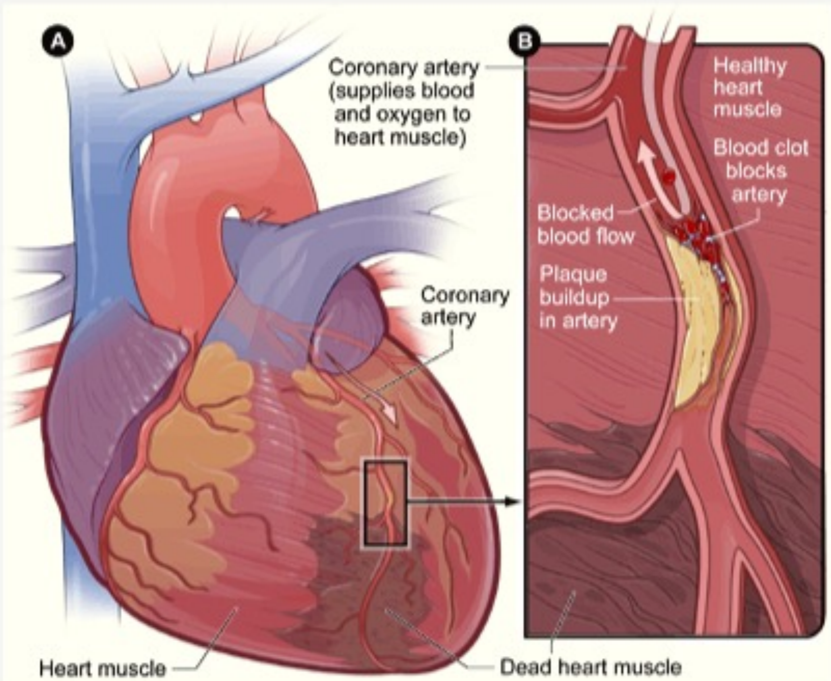
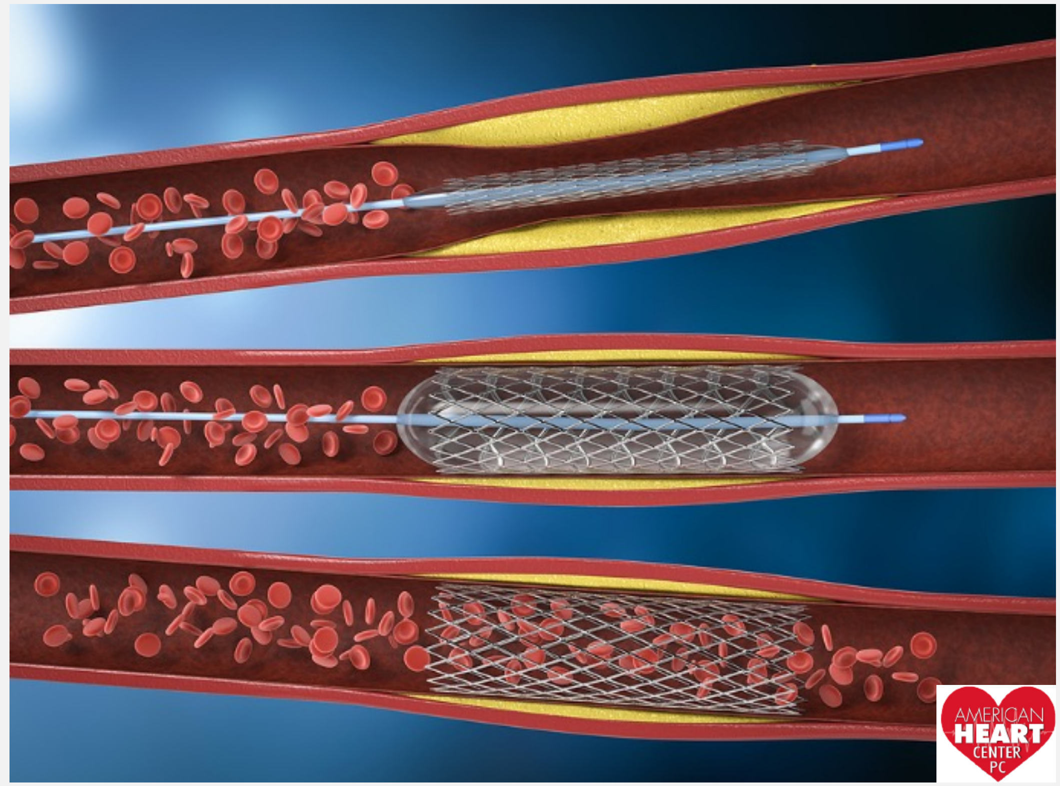


Figure A is an overview of a heart and coronary artery showing damage (dead heart muscle) caused by a heart attack. Figure B is a cross-section of the coronary artery with plaque buildup and a blood clot.

SOURCE: National Heart, Lung, and Blood Institute, National Institutes of Health

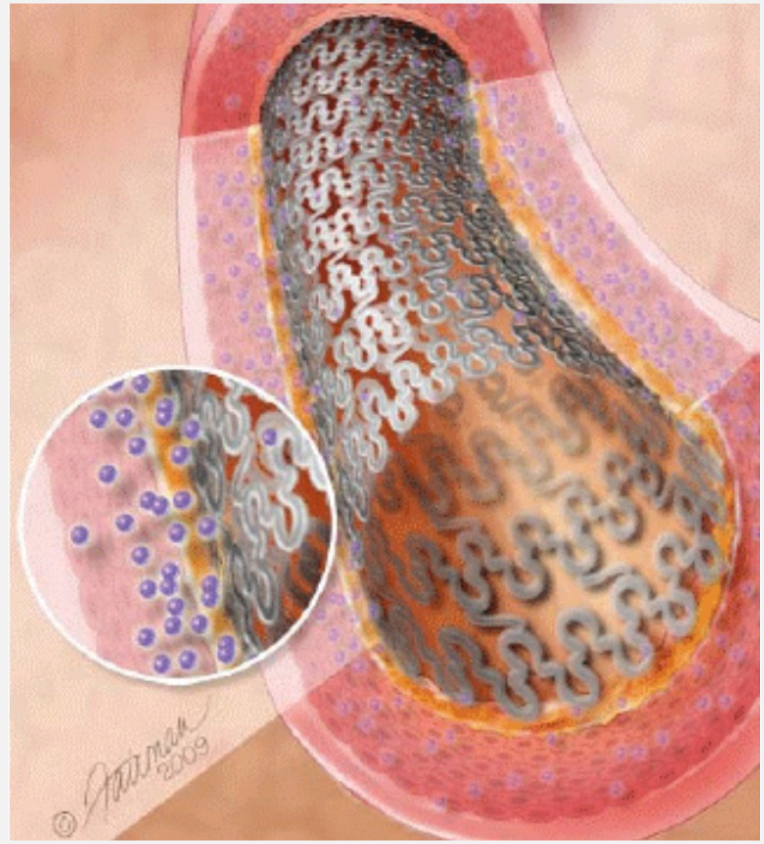


Angioplasty = repair of the blood vessel

Restenosis ~50%

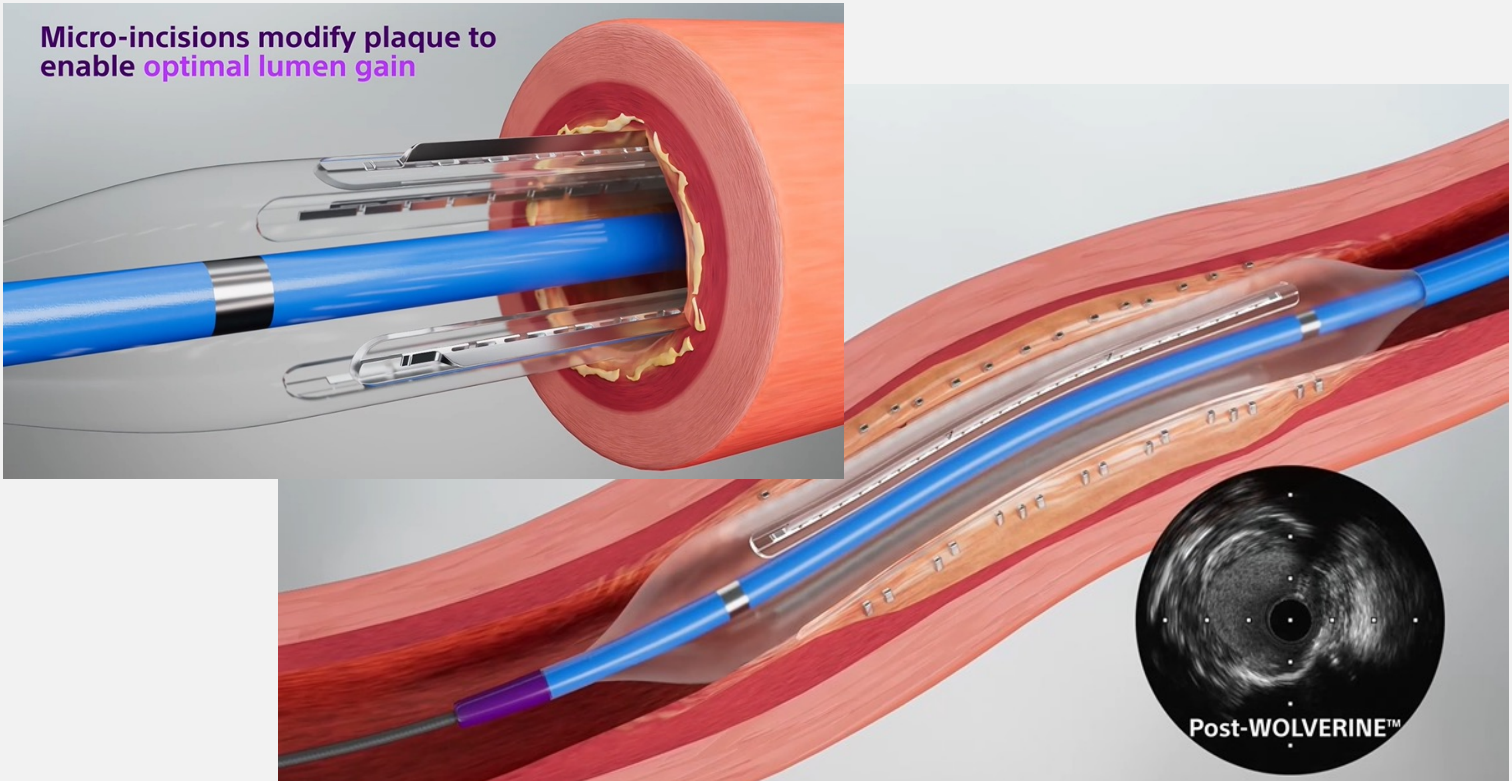
Restenosis ~10-20%

Ash heap of history

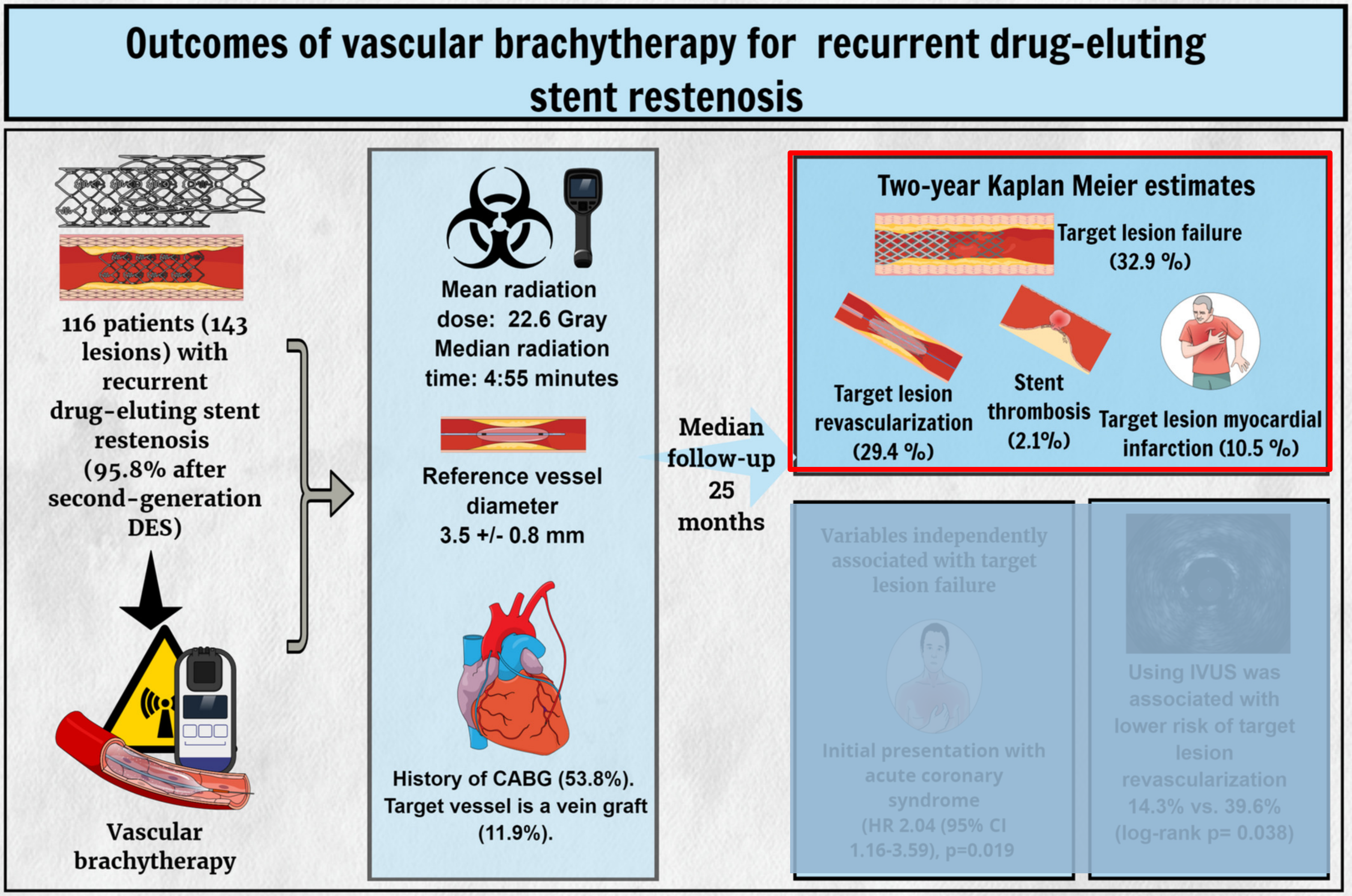


~60K angioplasties x 8% =
4800 per year

In stent failure after angioplasty + drug eluting stent?



Study	Year	Sample Size	Angiographic Stenosis, %	Stent Type	Pattern of ISR, % (n)	Treatments	DAPT Type and Duration	Follow-Up	Study Finding
PEPCAD DES[112]	2012	110	≥70 or ≥50 and ischemia	DES	Focal: 52.1 (111); diffuse: 43.7 (93); proliferative: 4.2 (9)	PCB vs PB	Aspirin 100 mg daily indefinitely + clopidogrel 75 mg daily for 6 mo	6 mo	• LLL: 0.43 ± 0.61 mm vs 1.03 ± 0.77 ($P < 0.001$) • Restenosis: 17.2% vs 58.1% ($P < 0.001$) • MACE: 16.7% vs 50.0% ($P < 0.001$)
ISAR DESIRE 3[71]	2013	402	≥50	DES	Focal: 66.8 (334); diffuse: 27.6 (138); proliferative: 1.4 (7); occlusive: 4.2 (21)	PEB vs PES and PEB/PES vs PB	Aspirin 200 mg daily indefinitely + oral platelet ADP-receptor antagonist ≥6 mo	Angiographic: 6-8 mo; clinical: 12 mo	• Diameter stenosis (PEB vs PES): 38.0% vs 37.4% (P for noninferiority = 0.011) • Diameter stenosis (PB): 54.1% (P for superiority [PEB and PES vs PB]: <0.0001 for both comparisons)
Habara et al[67]	2013	210	≥50%	BMS (58%) DES (42%)	Focal: 52.1 (111); diffuse: 43.7 (93); proliferative: 4.2 (9)	PCB vs PB	Aspirin 100 mg daily + ticlopidine 200 mg daily or clopidogrel 75 mg daily for ≥3 mo	Angiographic and clinical: 6 mo	• TVF: 6.6% vs 31.0% ($P < 0.001$) • Restenosis: 4.3% vs 31.9% ($P < 0.001$) • LLL: 0.11 ± 0.33 vs 0.49 ± 0.50 mm ($P < 0.001$)
PEPCAD China ISR[94]	2014	215	≥70 or ≥50 and ischemia	DES	Focal: 63.3 (140); diffuse: 19.5 (43); proliferative: 15.4 (34); occlusive: 1.8 (4)	PCB vs PES	Aspirin 100 mg daily indefinitely + clopidogrel 75 mg daily for ≥12 mo	Angiographic: 9 mo; clinical: 12 mo	• 9-mo in-segment LLL: 0.46 ± 0.51 vs 0.55 ± 0.61 mm (P for noninferiority = 0.0005) • 12-mo TLF: 16.5% vs 16.0% ($P = 0.92$)
DARE[113]	2018	278	>50	DES	Focal: 42.4 (118); diffuse: 27 (75); proliferative: 6.5 (18); occlusive 5 (14)	PEB vs EES	Aspirin for lifelong + $P2Y_{12}$ inhibitor for 12 mo	Angiographic: 6 mo; clinical: 12 mo	• In-segment MLD: 1.71 ± 0.51 vs 1.74 ± 0.61 ($P = 0.65$) • MACE: 10.9% vs 9.2% ($P = 0.66$)
BIOLUX[114]	2018	229	>50	DES	Focal: 68.8 (167); diffuse: 28 (68); proliferative: 2.5 (6); occlusive: 0.4 (1)	PCB vs EES	Aspirin + $P2Y_{12}$ inhibitor per local standard practice	Angiographic: 6 mo; clinical: 12 mo	• In-stent LLL: 0.03 ± 0.40 vs 0.20 ± 0.70 mm (difference: −0.17 ± 0.52 mm; P for noninferiority < 0.0001) • TLF: 16.7% (95% CI: 11.6%-23.7%) vs 14.2% (95% CI: 7.9%-24.7%; $P = 0.65$)



Cathet Cardio Intervent, Volume: 97, Issue: 1, Pages: 32-38, First published: 13 January 2020, DOI: (10.1002/ccd.28716)

ORIGINAL ARTICLE

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

See Editorial by Kleiman

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Samit Bhatheja, MD*
Usman Baber, MD, MS
Safwan Kezbor, CCRP
Aditi Chincholi, MBBS
Surbhi Chamaria, MD
Michael Buckstein, MD
Richard Bakst, MD
Annapoorna Kini, MD, MRCP

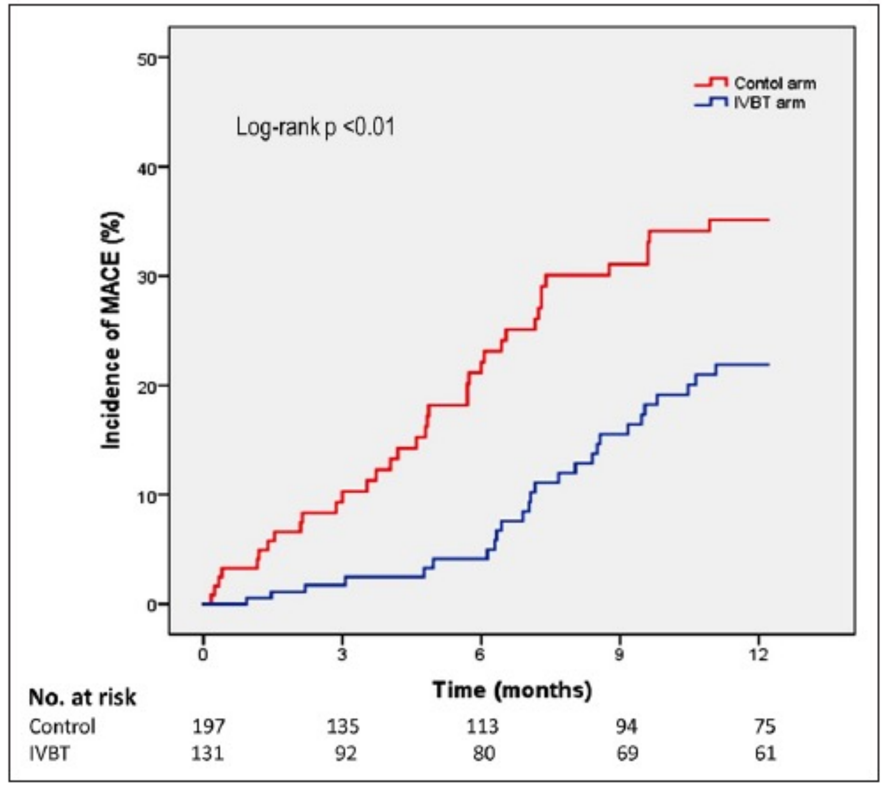
BACKGROUND: Because of the widespread acceptance of percutaneous coronary intervention with drug-eluting stents as an effective treatment strategy for in-stent restenosis, it is common to encounter multimetal layer stent restenosis in the recent years. This study aimed to evaluate the clinical outcomes of such patients treated with intravascular brachytherapy (IVBT) in comparison with other percutaneous options.

METHODS AND RESULTS: We enrolled patients who underwent

Clinical Outcomes at 1-Year Follow-Up

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

vas defined as a composite of death from any cause, MI, and target vessel revascularization. IVBT indicates ir apy; MACE, major adverse cardiac events; MI, myocardial infarction; ST, stent thrombosis; TLR, target lesion revasc arget vessel revascularization.



TECHNOLOGY REPLACEMENT

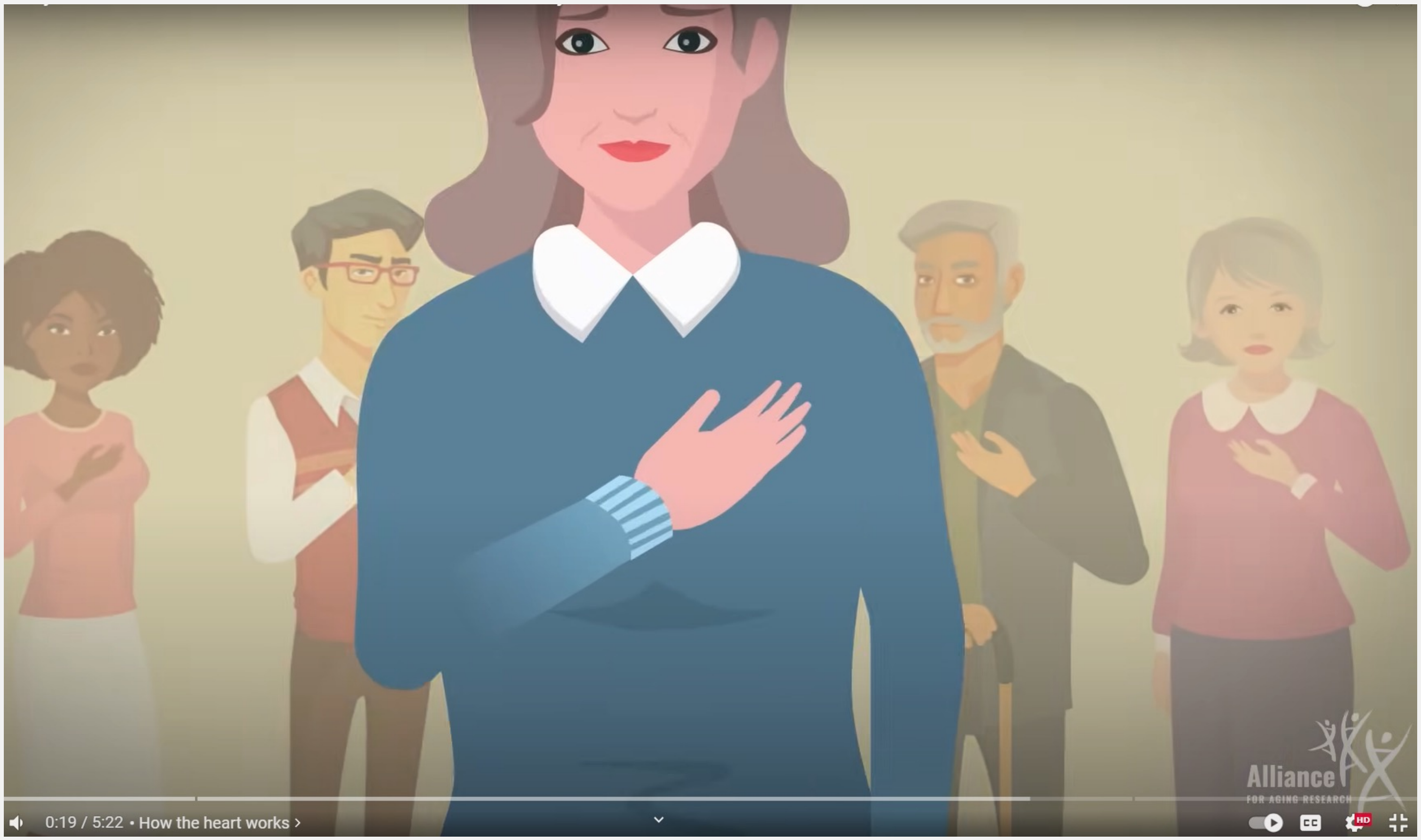
- Faster
- Less expensive
- Possibly more effective
- Less burdensome regulatory environment

Radionuclide brachytherapy → Hypothetical Electronic (LWFA) brachytherapy

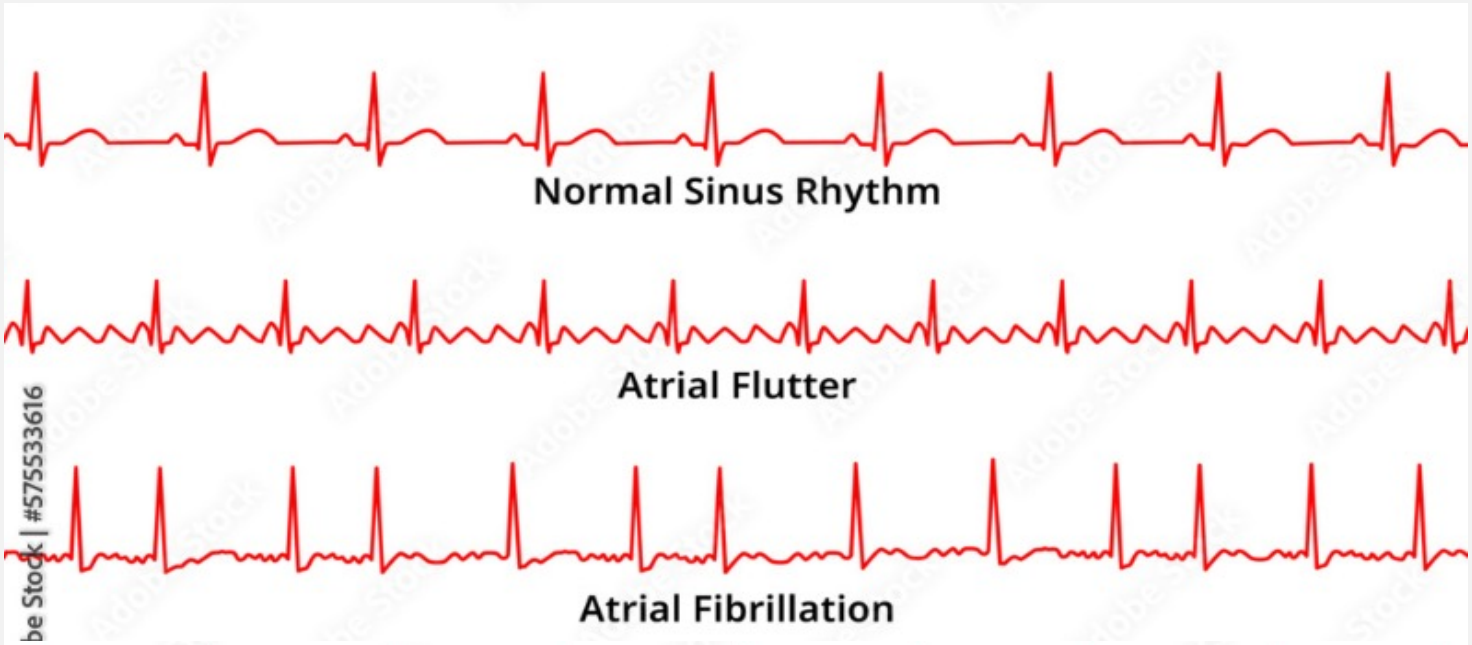
WHAT CAN YOU DO WITH A NOVEL RADIATION SOURCE?

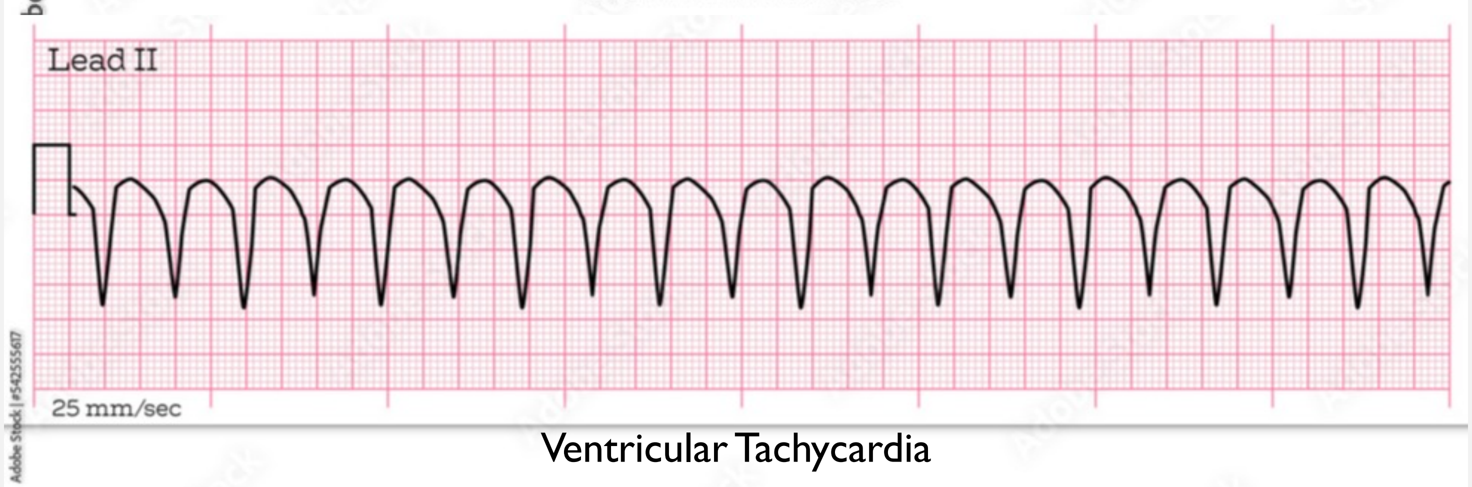
	Replace existing radiation technology	Replace other technology	New applications
Indications	Same	Same or new	New
Toxicities	Less	Same or less	TBD
Cost	Same or less	Same or less	TBD
Example(s)	▪ Radionuclide brachytherapy ▪ IOERT ▪ Superficial electron therapy	▪ Cardiac arrythmia ablation ▪ Radiofrequency ablation	▪ TBD

NON DESTRUCTIVE ABLATION FOR CARDIAC ARRYTHMIAS



0:19 intro
2:20 ventricular

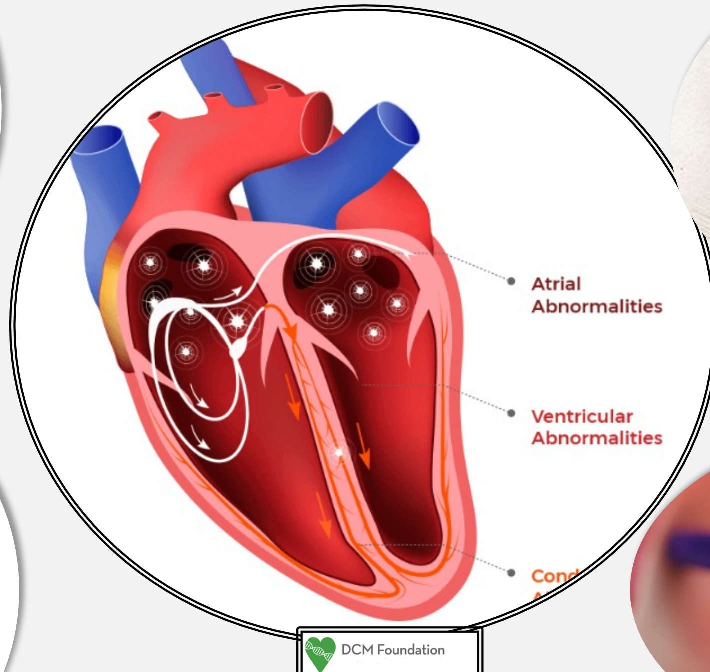


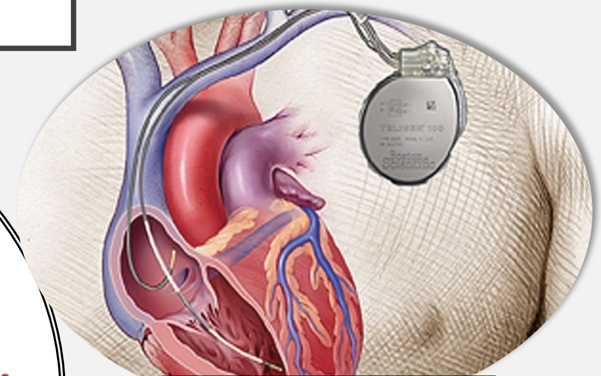


Ventricular Tachycardia

MANAGEMENT

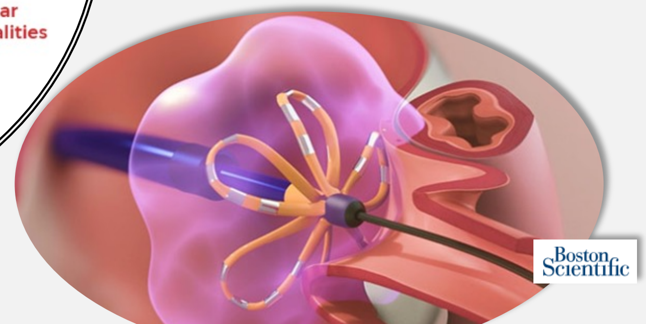
Medications



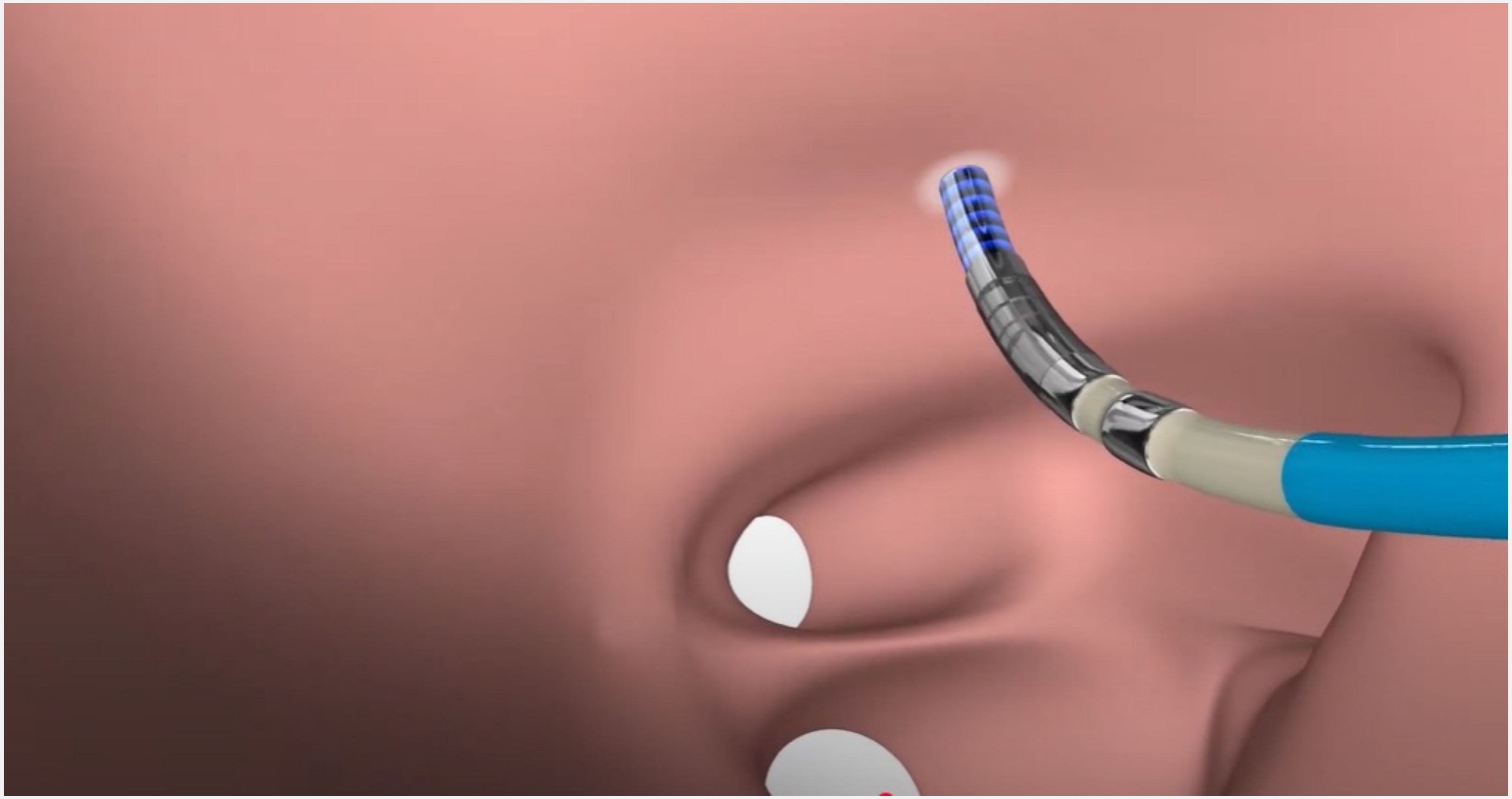


Implantable devices

Heart healthy lifestyle



Catheter ablation
~70,000 procedures per year



0:40 to 1:26

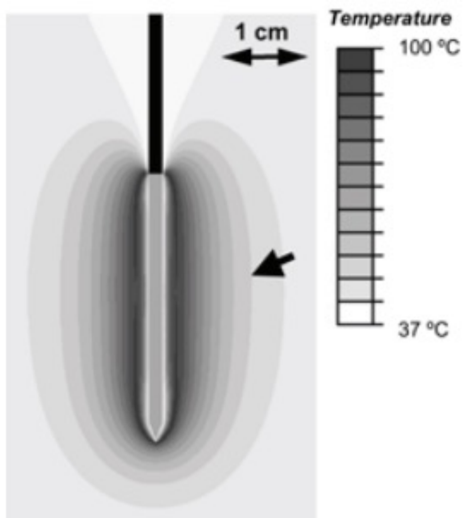
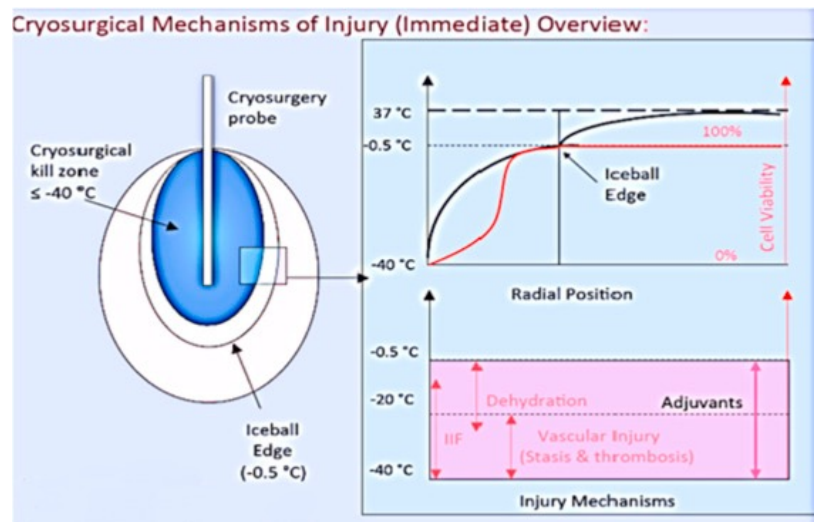


FIGURE 3. Tissue-temperature profile from a computer simulation at the end of a 12-min RF ablation with a cooled-needle electrode (same as in Fig. 8B). The black part of the electrode is electrically insulated, and heating due to RF current results around the exposed metal electrode (electrode tip, shown in gray). Black arrowhead marks the boundary of the ablation zone (~50°C).

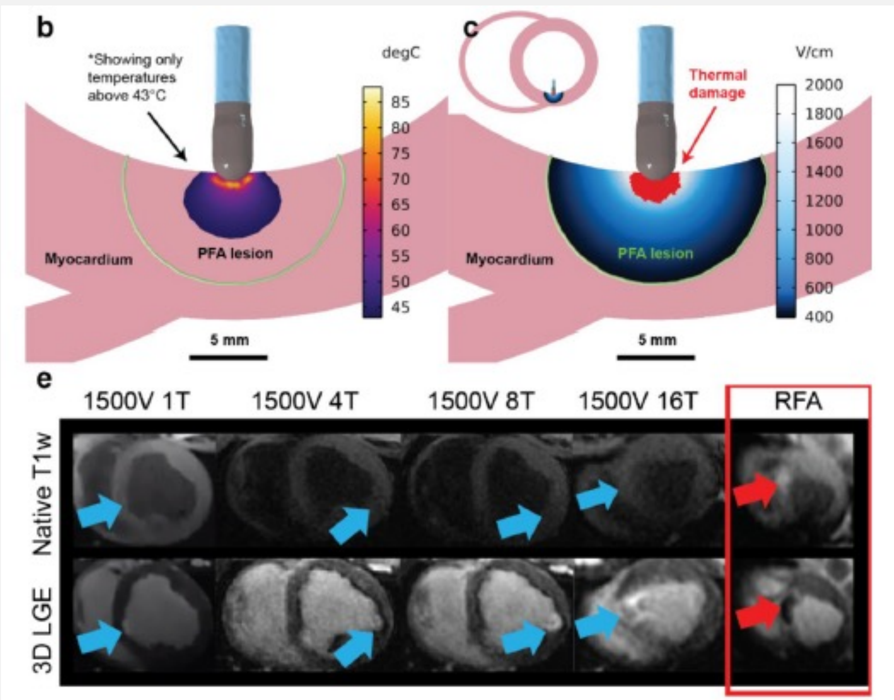
Haemmerich, D. Critical Reviews in Biomedical Engineering, 2010

Radio frequency ablation



Avitall, B and Kalinski, A. Heart Rhythm, 2015

Cryosurgery



Dukkipati, et al. J Am Coll Cardiology, 2017

Pulsed field ablation

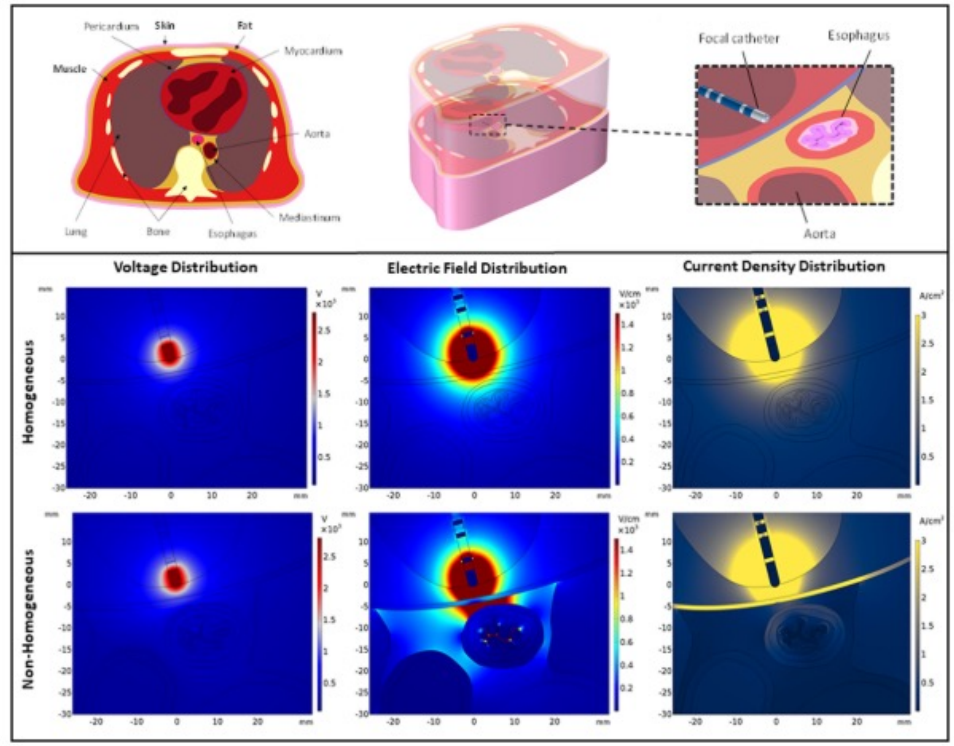
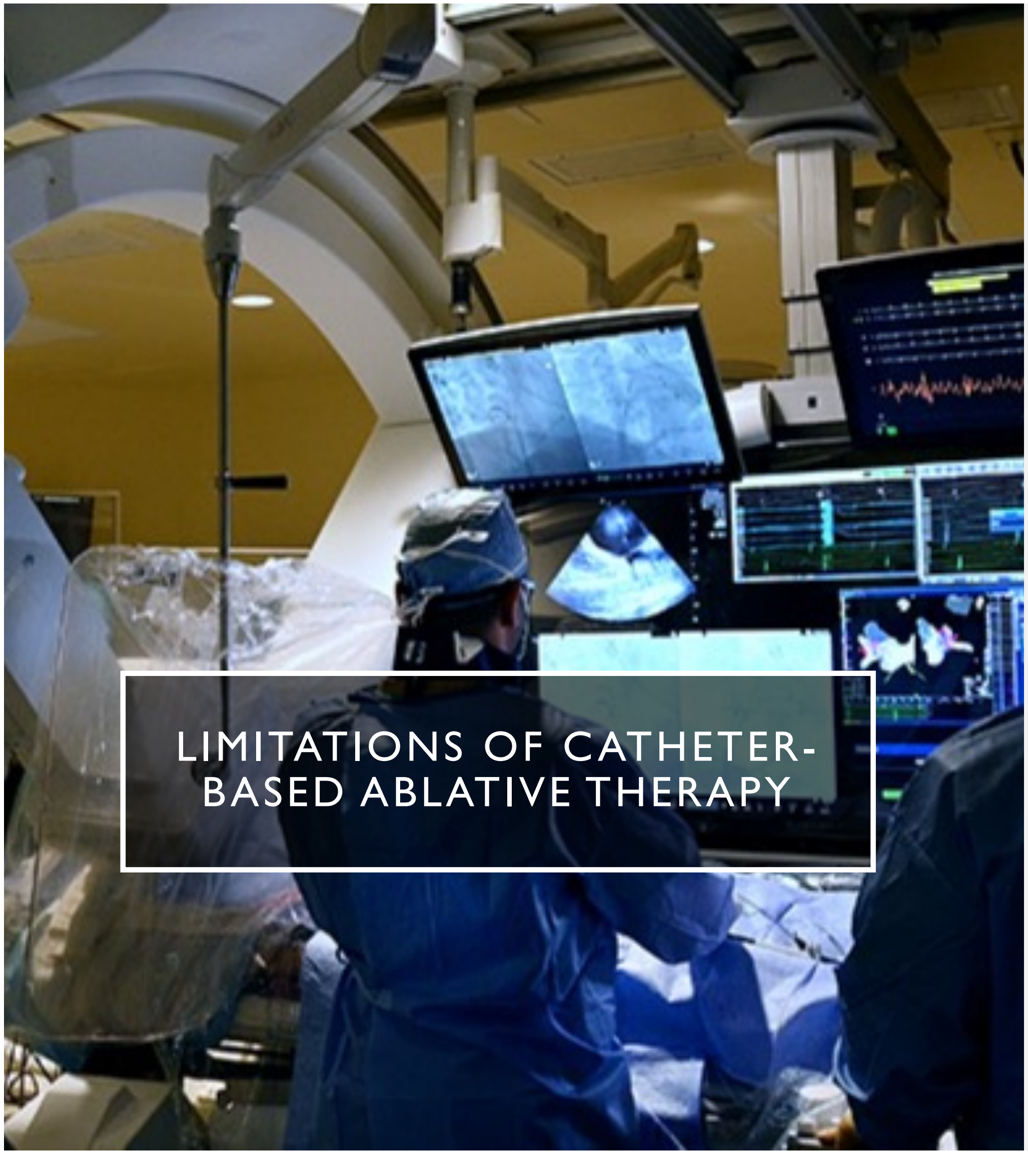


Figure 5. Numerical simulation of heterogeneous tissue environment. Top, A numerical simulation is generated to represent human anatomic geometry, with a representative monopolar focal ablation catheter placed on the posterior wall of the left atrial. Voltage, electric field, and current density distributions for homogeneous (**center**) and heterogeneous (**bottom**) tissue electrical properties from a clinically relevant pulsed electrical field delivered protocol, demonstrating the distributive nature of the pericardial fluid surrounded by the pericardial sac.

Verma, et al. , Circulation: Arrhythmia and Electrophysiology 2017



LIMITATIONS OF CATHETER-BASED ABLATIVE THERAPY

- Prior ablations insufficiently effective
- Unable to reach target substrate(s)
- Proximity of target substrate(s) to critical structures
- Size of target substrate(s)
- Physiologically unable to tolerate cath procedure

NON DESTRUCTIVE TISSUE ABLATION?

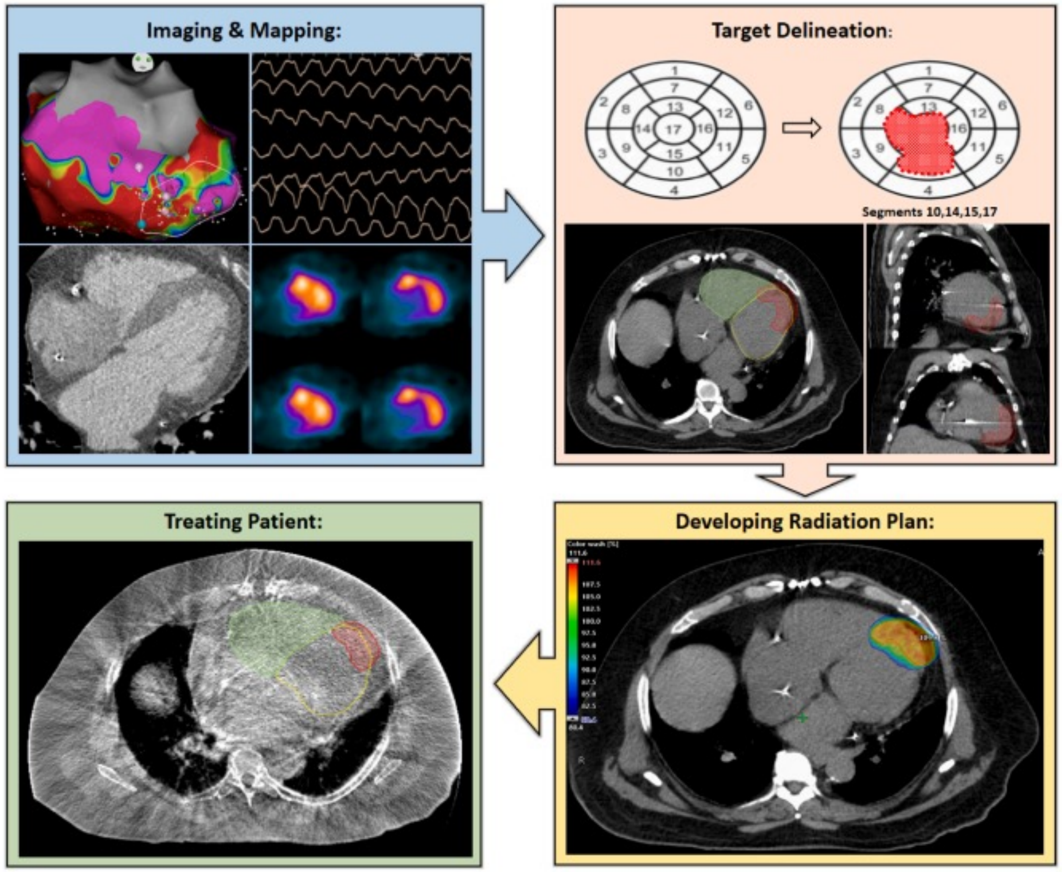


Fig. 3. Cardiac Radioablation Treatment Workflow. Blue Panel: Identifying and Mapping the CRA Target. In clockwise order, non-invasive EKG, SPECT, Cardiac CT w/ contrast, and endocardial catheter-based voltage map used to localize the ventricular scar prior to radiation planning. Orange Panel: Target Delineation. Top panel shows 17-segment left ventricular model targeting 4 segments identified during mapping. Bottom panel with radiation therapy planning software showing PTV (red) contoured within the left and right ventricle. Yellow Panel: Developing a Radiation Plan. External beam planning software showing dose color wash of PTV (red) from 80 to 110% of prescription dose. Green Panel: Treating the Patient. Aligning PTV using cone beam CT on the day of treatment. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Siedow, et al. Clinical Translational Radiation Oncology, 2021

Table 2 Summary of the VT burden reduction in evaluable patients treated in prospective studies investigating STAR for the treatment of therapy-refractory VT

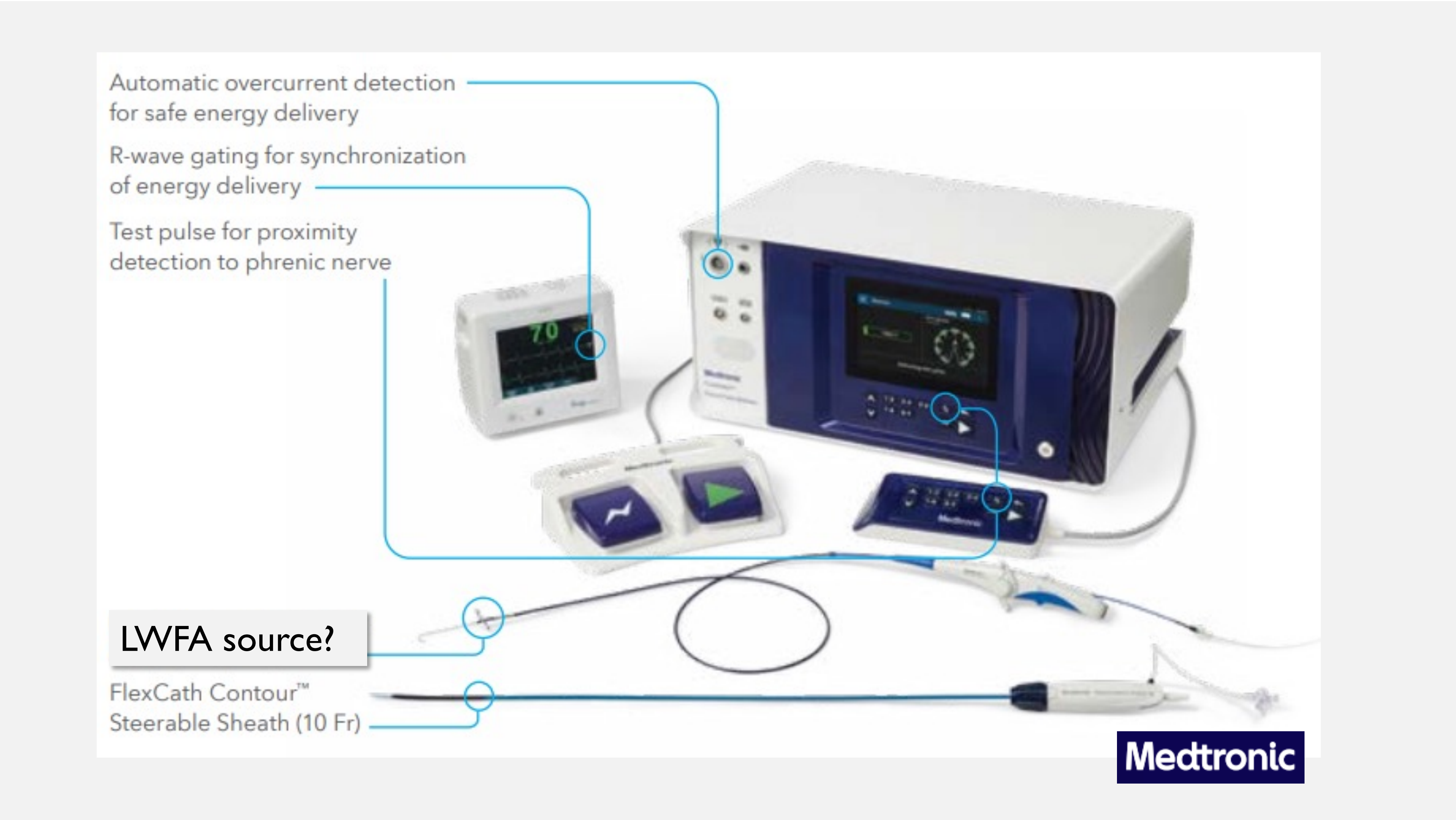
Study	N (evaluable)	VT burden definition used for this analysis	Adjusted time frame for VT burden reduction calculation	≥95% VT burden reduction, % (n)	≥75% VT burden reduction, % (n)	≥50% VT burden reduction, % (n)
Robinson et al[1]	18	ICD-treated VT episodes or 24-h PVC burden	6 mo before STAR compared with 6 mo after, excluding events in the first 6 wk	61% (11)	89% (16)	94% (17)
Molon et al[21,*]	5	ICD-treated VT episodes	6 mo before STAR compared with 6 mo after, excluding events in the first 4 wk	60% (3)	60% (3)	100% (5)
Amino et al[25]	3	Treated VT episodes	6 mo before STAR compared with 6 mo after, excluding events in the first 6 wk	67% (2)	67% (2)	67% (2)
Arkles et al[19]	12	Treated VT episodes	6 mo before STAR compared with 6 mo after, excluding events in the first 6 wk	75% (9)	83% (10)	83% (10)
van der Ree et al[24,*]	6	Treated VT episodes	6 mo before STAR compared with 6 mo after, excluding events in the first 6 wk	33% (2)	100% (6)	100% (6)
Gianni et al[18]	4[†]	ICD-treated VT episodes	3 mo before STAR compared with 6 mo after, excluding events in the first 3 mo	25% (1)	25% (1)	75% (3)
Carbucicchio et al[20]	4	ICD-treated VT/VF episodes	3 mo before STAR compared with 6 mo after, excluding events in the first 3 mo	50% (2)	100% (4)	100% (4)
Miszczyk et al[23,*]	9[†]	ICD-treated VT episodes	3 mo before STAR compared with 6 mo after, excluding events in the first 3 mo.	80% (8)	80% (8)	90% (9)
Chang et al[26]	0	n/a	n/a	n/a	n/a	n/a
Krug et al[22]	0	n/a	n/a	n/a	n/a	n/a

ICD = implantable cardioverter-defibrillator; n/a = not applicable/available; PVC = premature ventricular contraction; STAR = stereotactic arrhythmia radioablation; VF = ventricular fibrillation; VT = ventricular tachycardia.

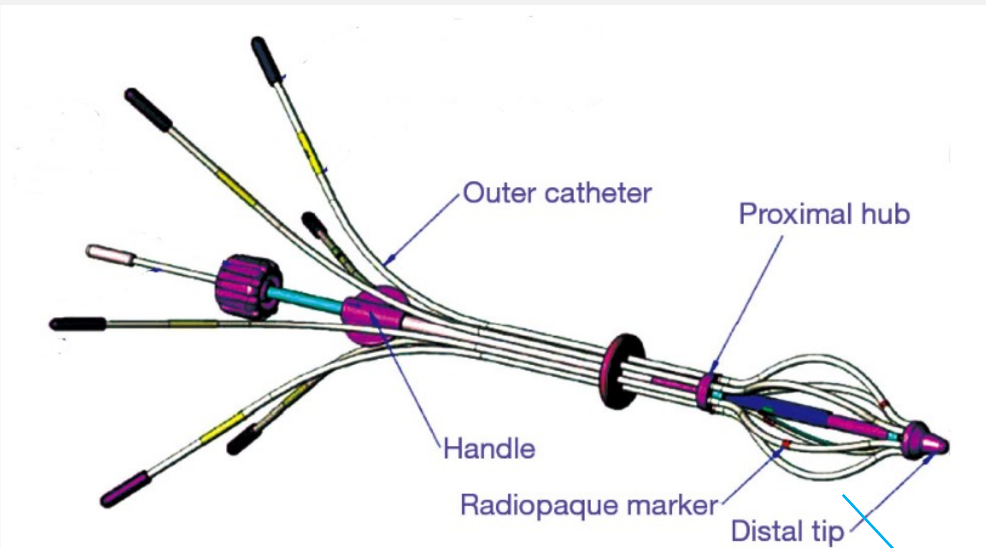
*Additional data retrieved for this analysis through correspondence with the authors.

†One patient was excluded because of the lack of treated VT episodes during the pre-STAR period within the adjusted time frame.

Micsuk, et al Heart Rhythm, 2024


Automatic overcurrent detection
for safe energy delivery
R-wave gating for synchronization
of energy delivery
Test pulse for proximity
detection to phrenic nerve
LWFA source?
FlexCath Contour™
Steerable Sheath (10 Fr)
70
Medtronic

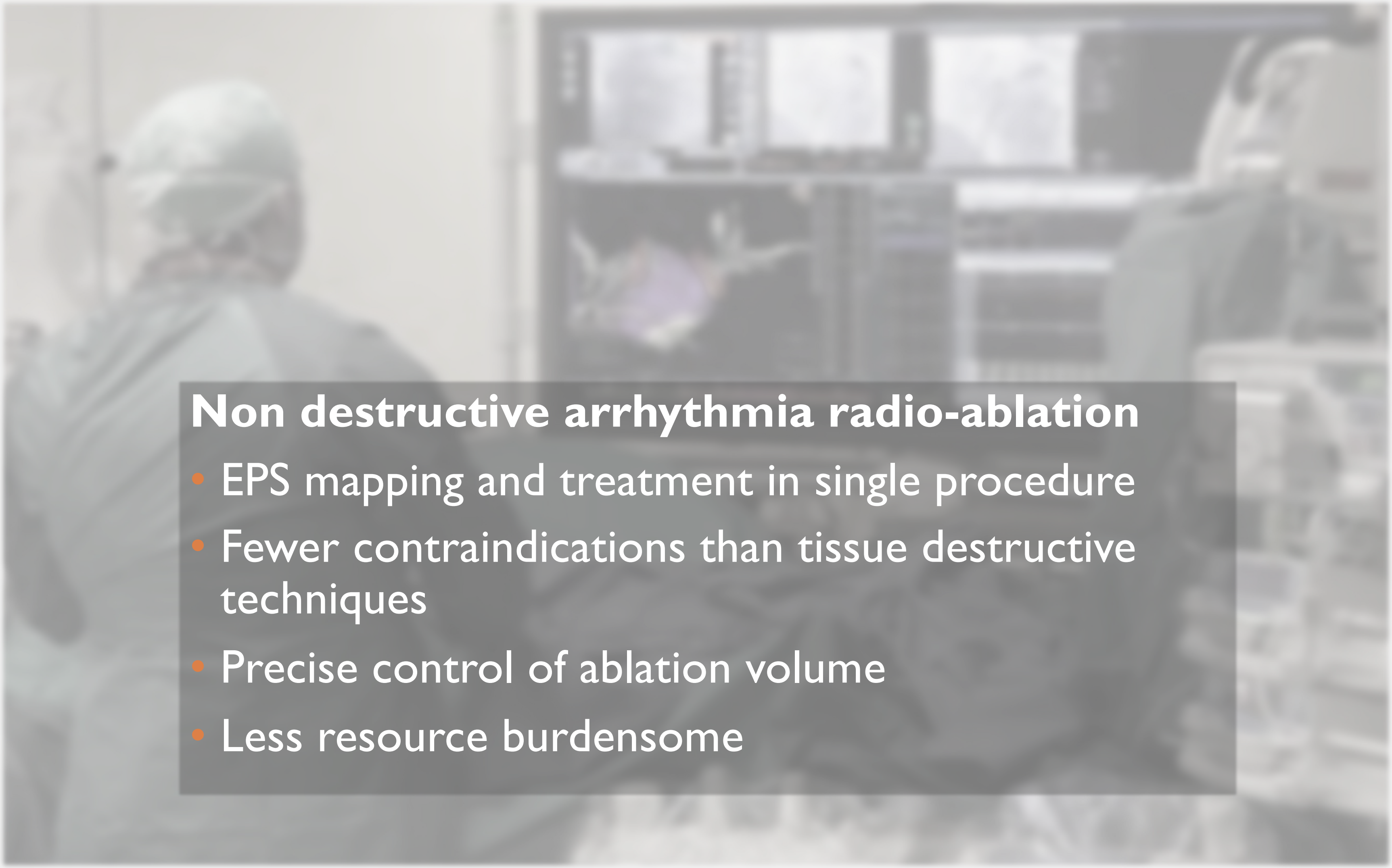
Hypothetical LWFA cardiac ablation devices



Volumetric radioablation (i.e. a-fib)

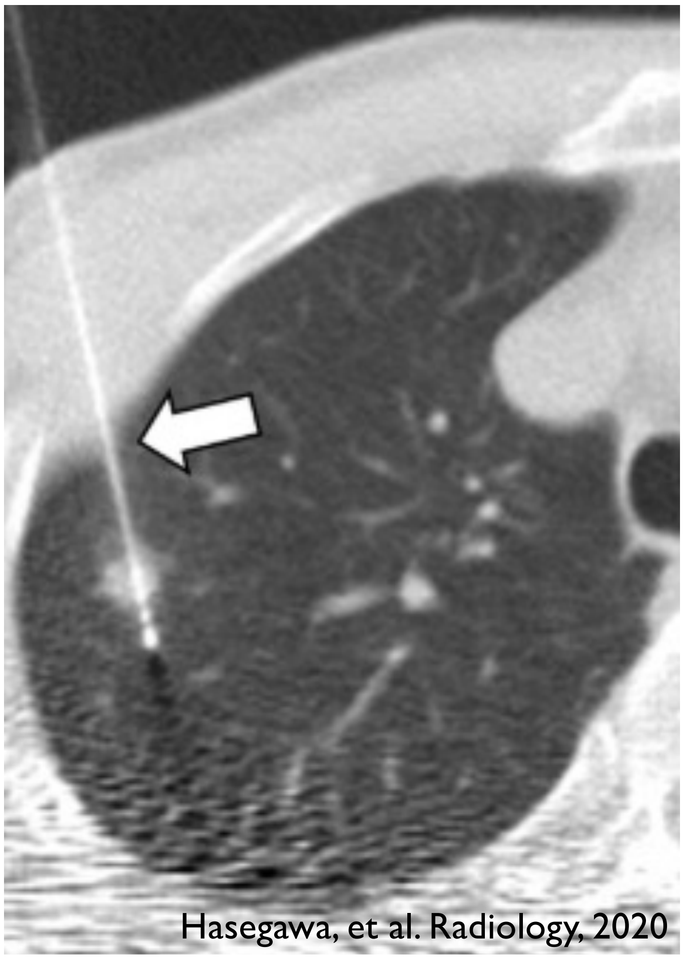
Point radioablation (i.e. V-tach)

LWFA channel source(s)
EPS sensors
Ion chambers

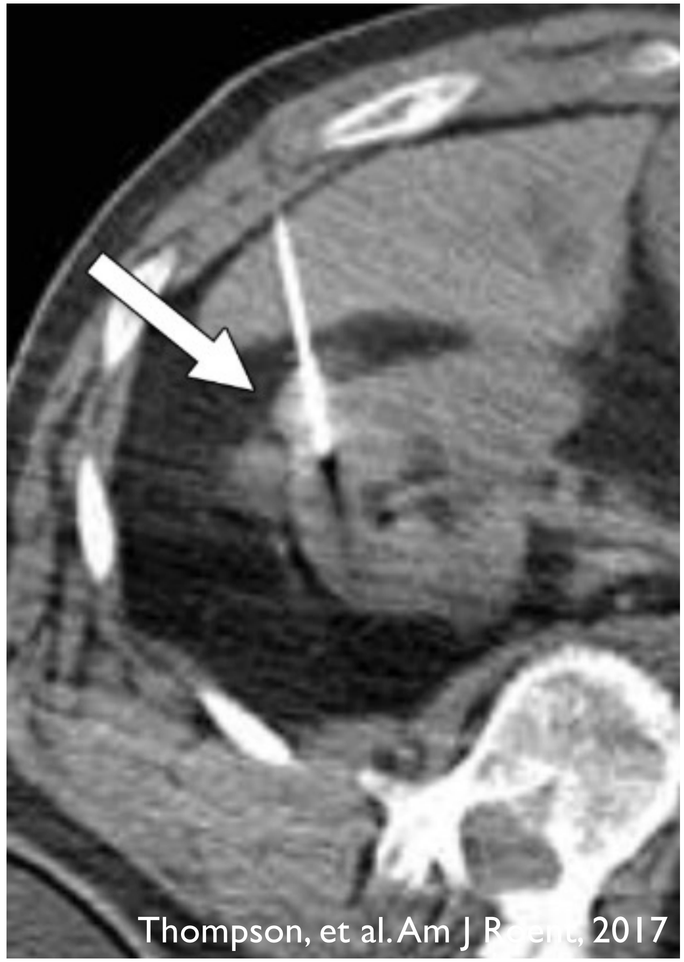


Non destructive arrhythmia radio-ablation

- EPS mapping and treatment in single procedure
- Fewer contraindications than tissue destructive techniques
- Precise control of ablation volume
- Less resource burdensome

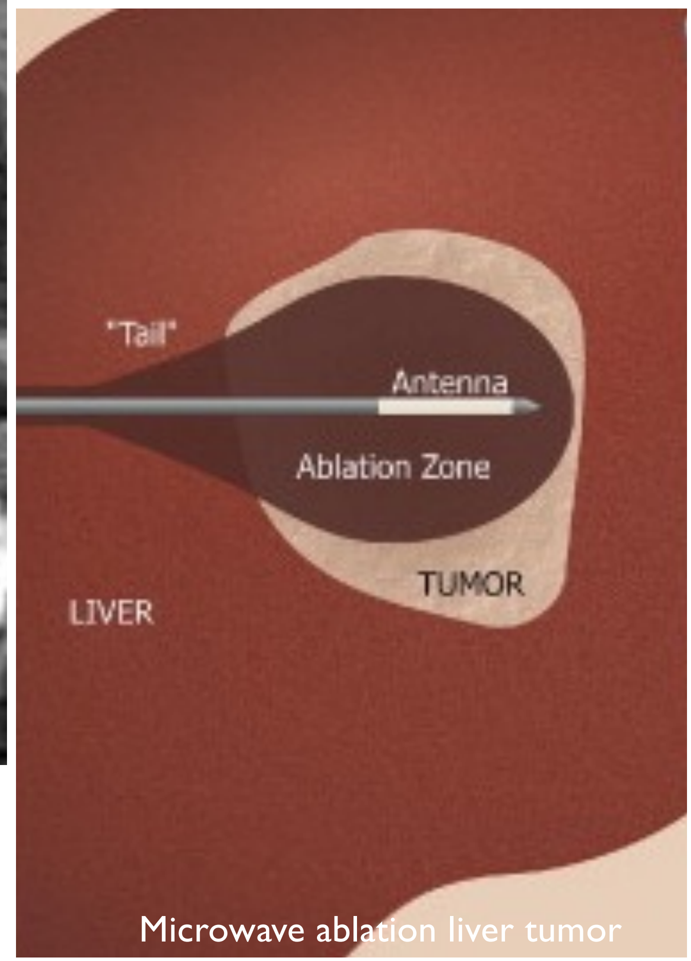


Hasegawa, et al. Radiology, 2020



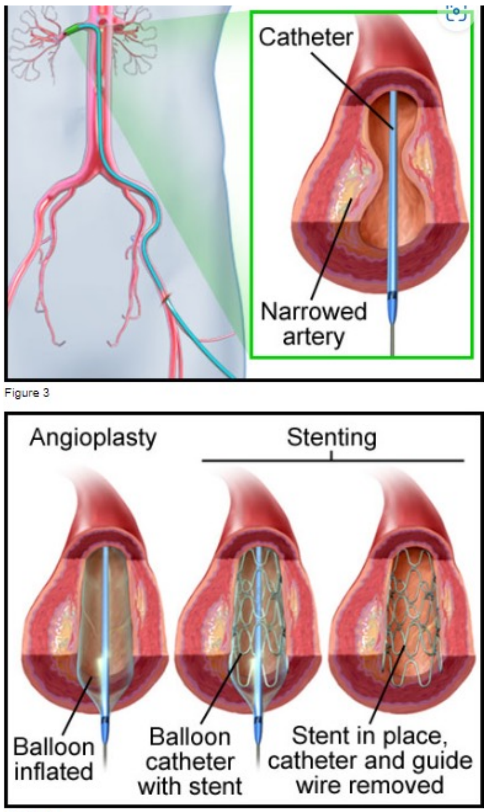
Thompson, et al. Am J Roent, 2017

Extra cardiac tissue ablation



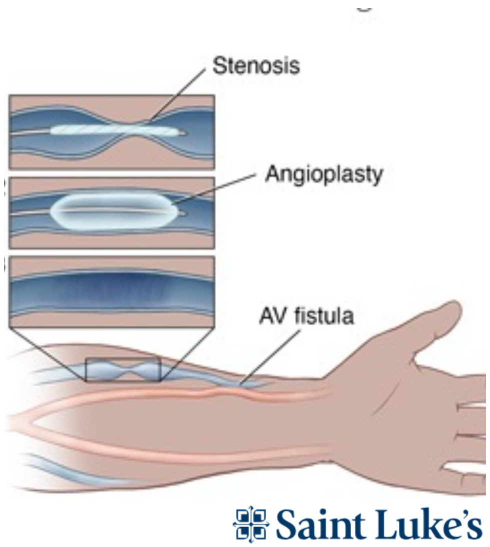
Microwave ablation liver tumor

Extra cardiac stent failures



Stent for renal artery stenosis

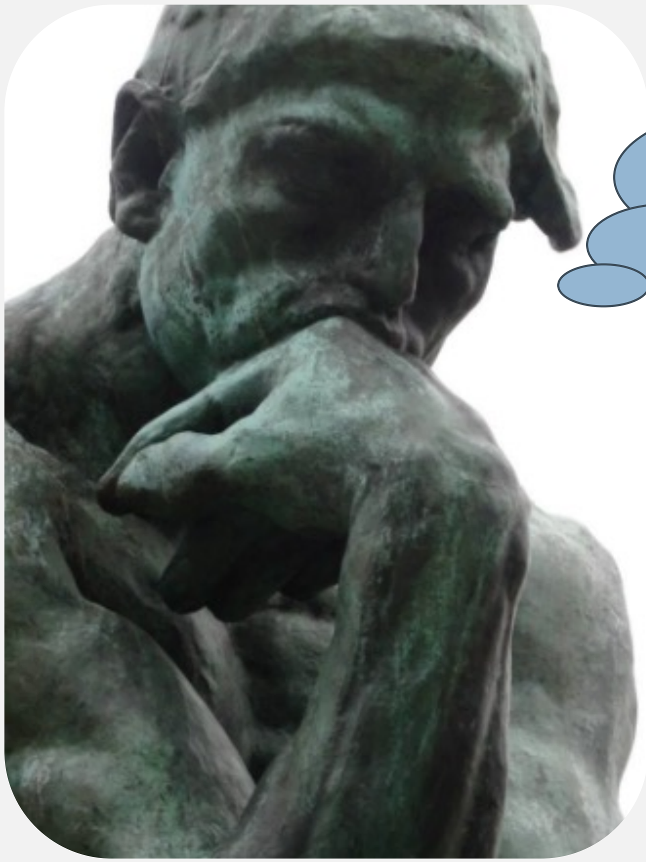
Biliary stent for strictures



AV fistula for dialysis

WHAT CAN YOU DO WITH A NOVEL RADIATION SOURCE?

	Replace existing radiation technology	Replace other technology	New applications
Indications	Same	Same or new	New
Toxicities	Less	Same or less	TBD
Cost	Same or less	Same or less	TBD
Example(s)	▪ Radionuclide brachytherapy ▪ IOERT ▪ Superficial electron therapy	▪ Cardiac arrythmia ablation ▪ Radiofrequency ablation	▪ TBD



I'm going to sit and come up with something completely brilliant

Note: everything here is speculation

Physical dimensions

- Miniature applicators
- Inside/along endoscope
- Inside/ along vascular catheter
- Handheld applicator

Power source

- No cooling system
- Wearable battery pack
- Implantable
- Autonomous (mobile) unit

Beam geometry

- Directional
- Steerable
- Dynamic control
- Point, line, plane, volume

Beam quality

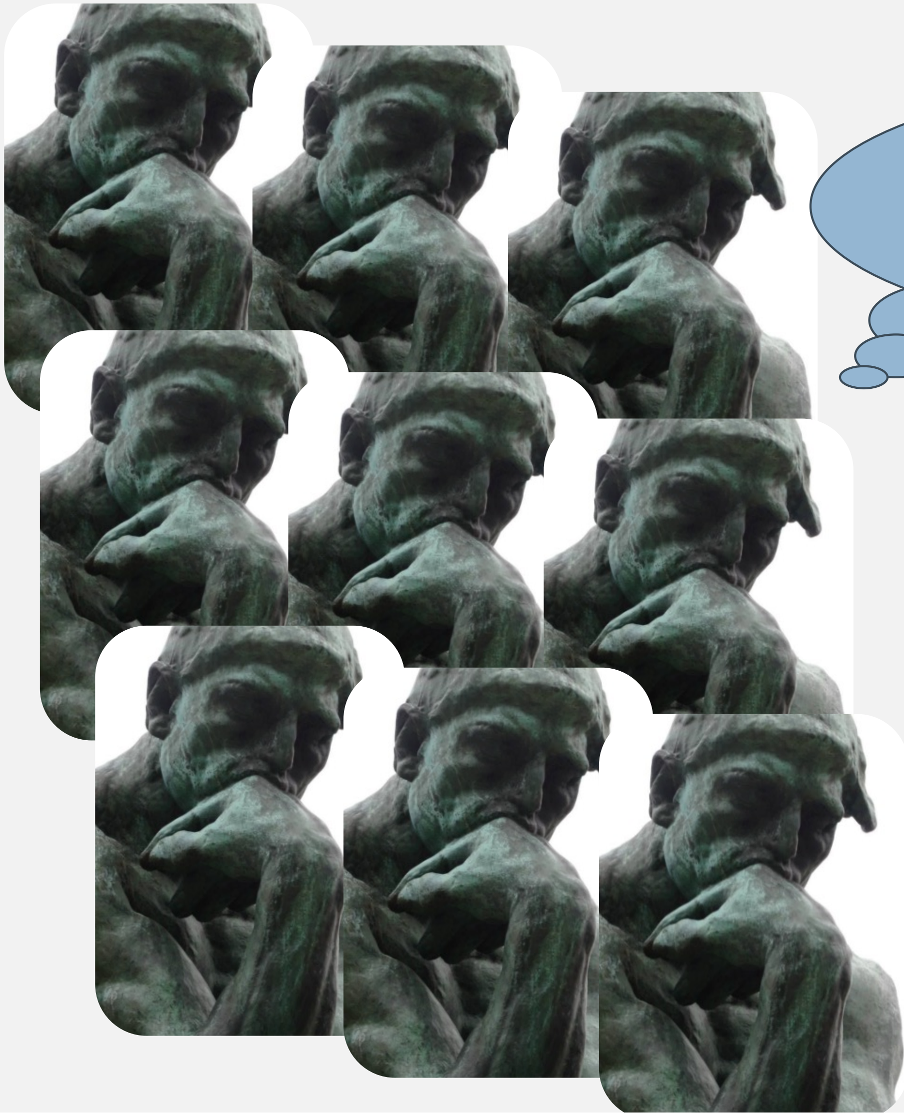
- Tunable
- Control pulse shape, duration, frequency
- Pulse rate
- Dynamic control

Electron beam activates clinical agent

- X-ray production (brehmstrahlung)
- Plasma produced by electron ionization
- In vivo polymeric biomaterial synthesis
- Anti-infective activity

Jurisdiction

- LWFA specific training for non radiation oncologists
- Regulated more like laser than radionucildes

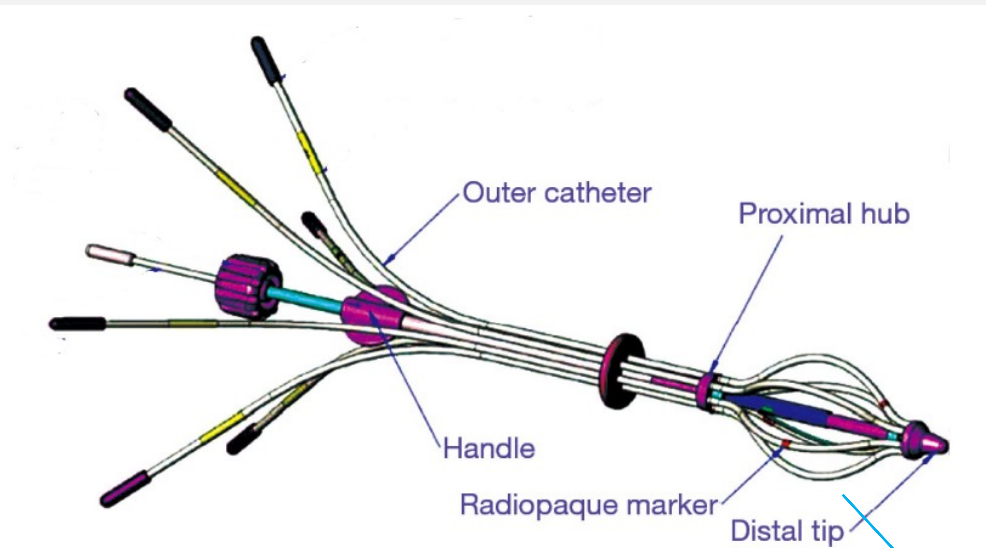


I'm going to brainstorm with colleagues

Thank you!

Questions?

Hypothetical LWFA cardiac ablation devices



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