Interventional Cardiology Drug-Eluting Stent Evolution Dedication for Advancement

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Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below

Affiliation/Financial Relationship	Company
Institutional Grant/Research Support	Biotronik, Boston Scientific, Medtronic CardioVascular, Medinol, Orbus Neich
Consulting Fees/Honoraria	Biotronik, Boston Scientific Corporation, Medtronic CardioVascular, Cardinal Health
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

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Evolution of Interventional Cardiology
Anything But Chance

First Palmaz-Schatz Stent in Human
December 31, 1987

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Evolution of Interventional Cardiology
Anything But Chance

December 1999, First in Human Cypher Sirolimus Eluting Stent

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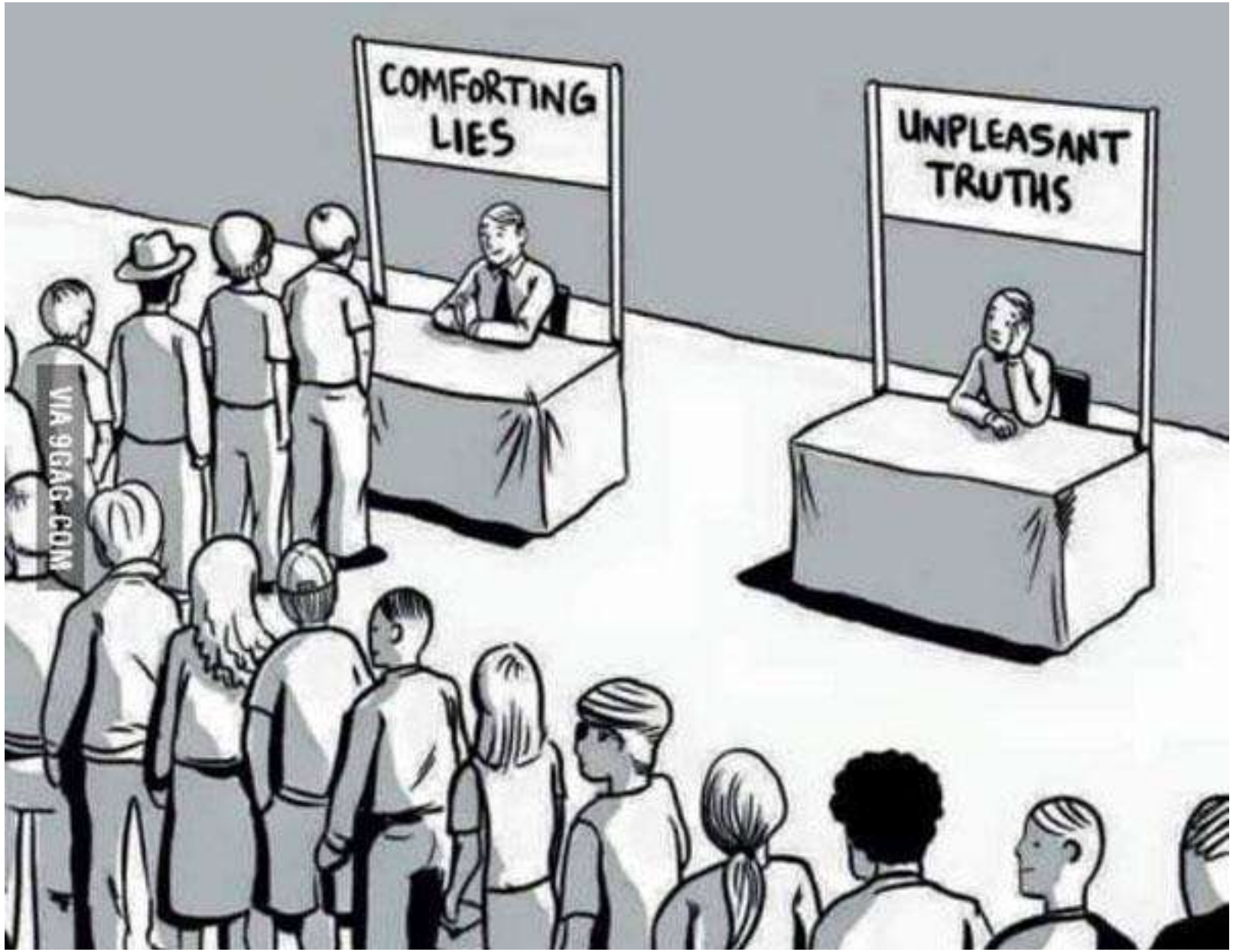

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What Do We Know About DES in 2018?

- Profound, durable reduction in need for repeat revascularization
- From RCTs, possibly lower MI, TLR and ST compared with BMS *and* BVS
- Lifelong, perhaps even 1 year, commitment to DAPT unfounded
- 'Off Label' does not mean 'Unstudied'
- Emerging differences in efficacy and safety endpoints between DES, no 'class effect'
- The story of safety and efficacy with DES does not stop at the primary endpoint

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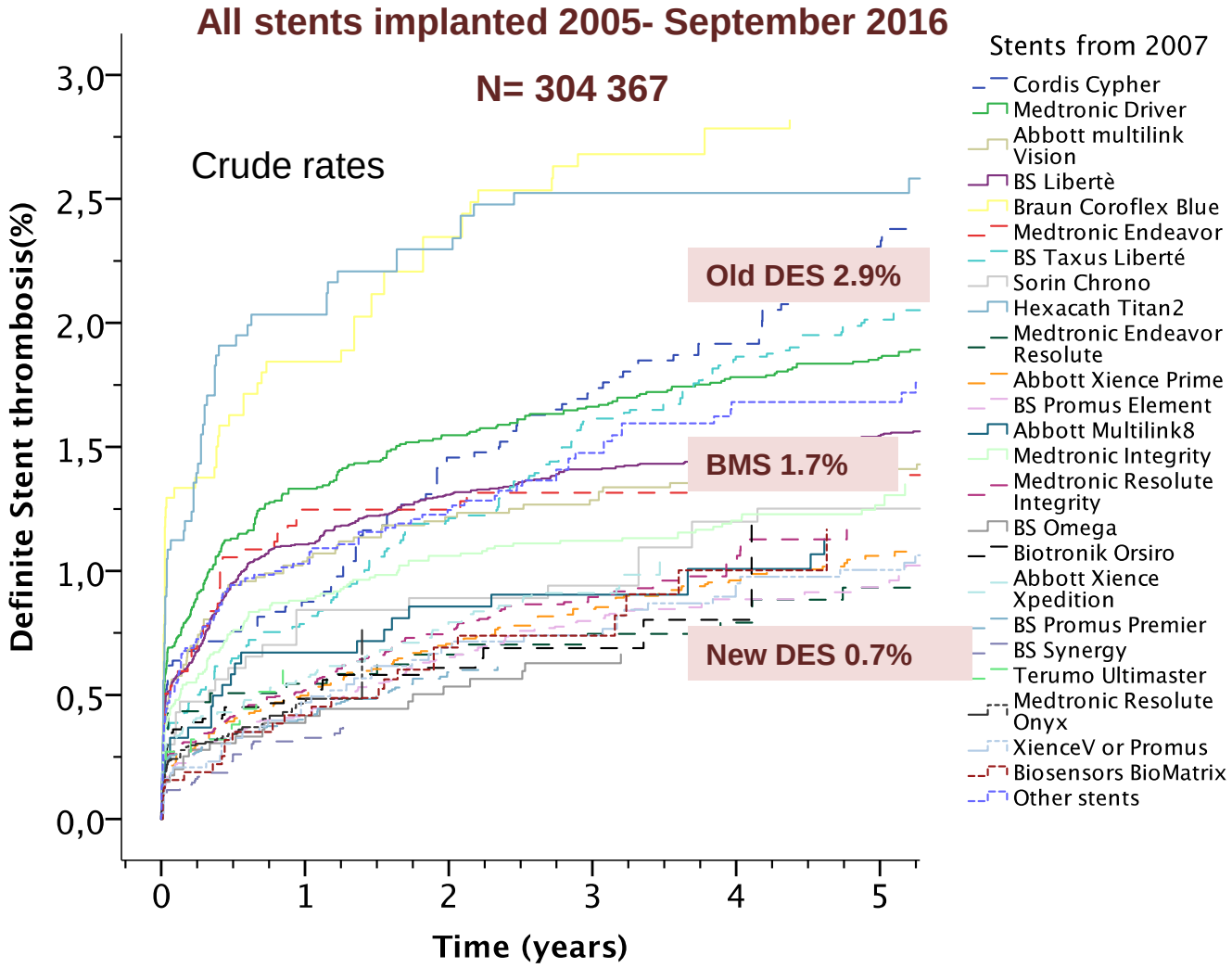
SCAAR Registry Definite ST for Contemporary DES



S. James, TCT 2017

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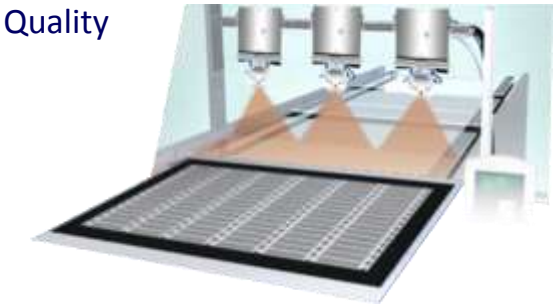
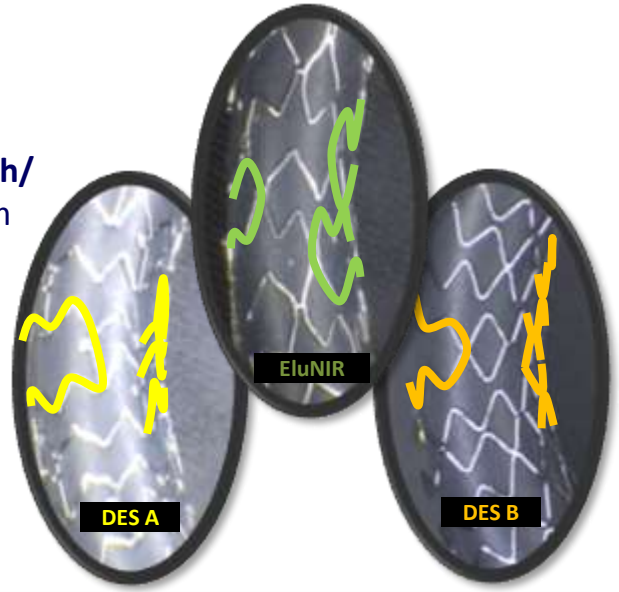
EluNIR™ Stent System

Flat manufacturing: Quality

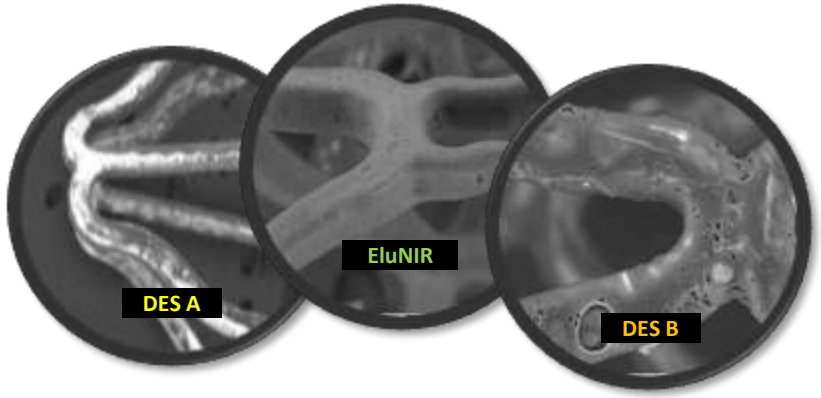


- *90µm CoCr WiZeCell design*
- *Ridaforolimus high therapeutic index drug*

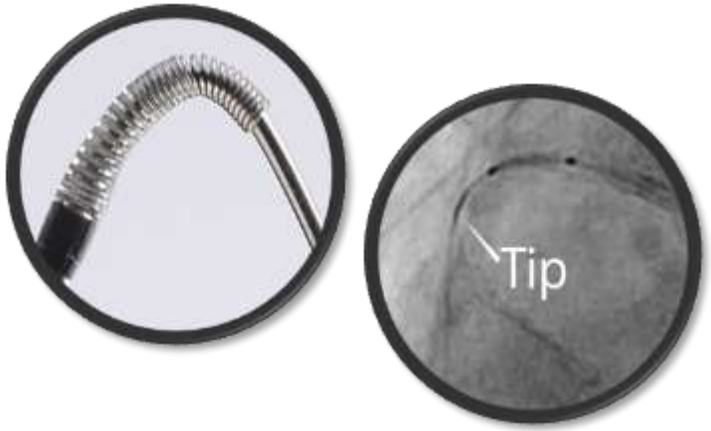
Variable strut width/ frequency: Uniform dosing



Elastomeric Polymer: Remains intact post elution



Spring tip: Pushable & visible



Medinol Ltd., Tel Aviv, Israel

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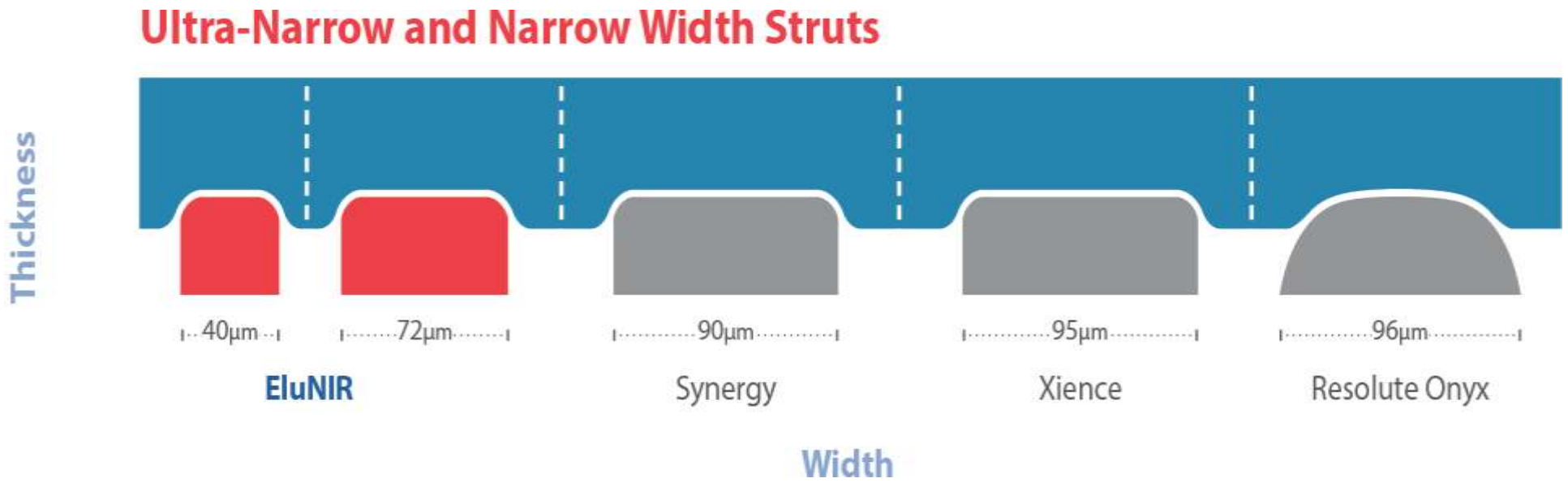
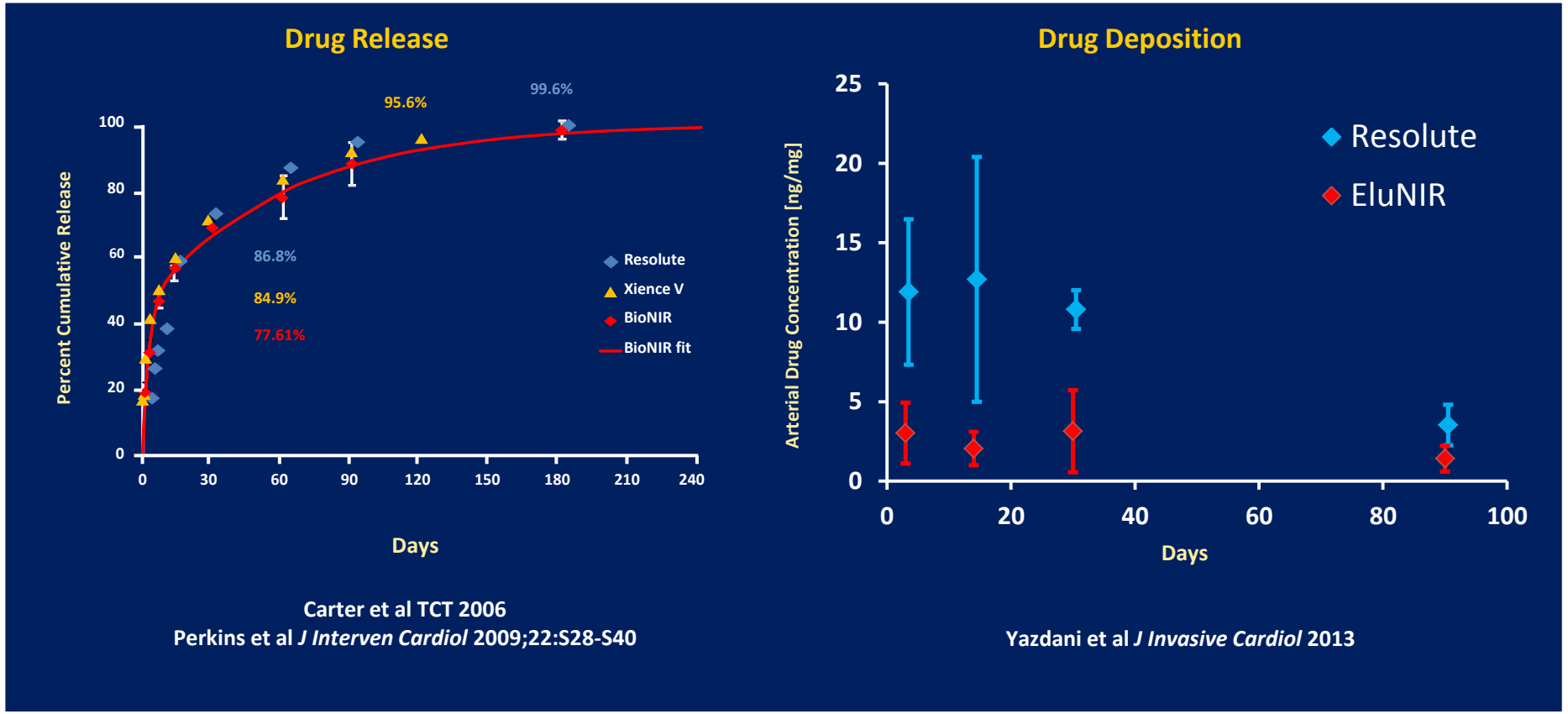
EluNIR™ Stent System



EluNIR™ System Pharmacokinetics



Kandzari et al. Circulation 2017

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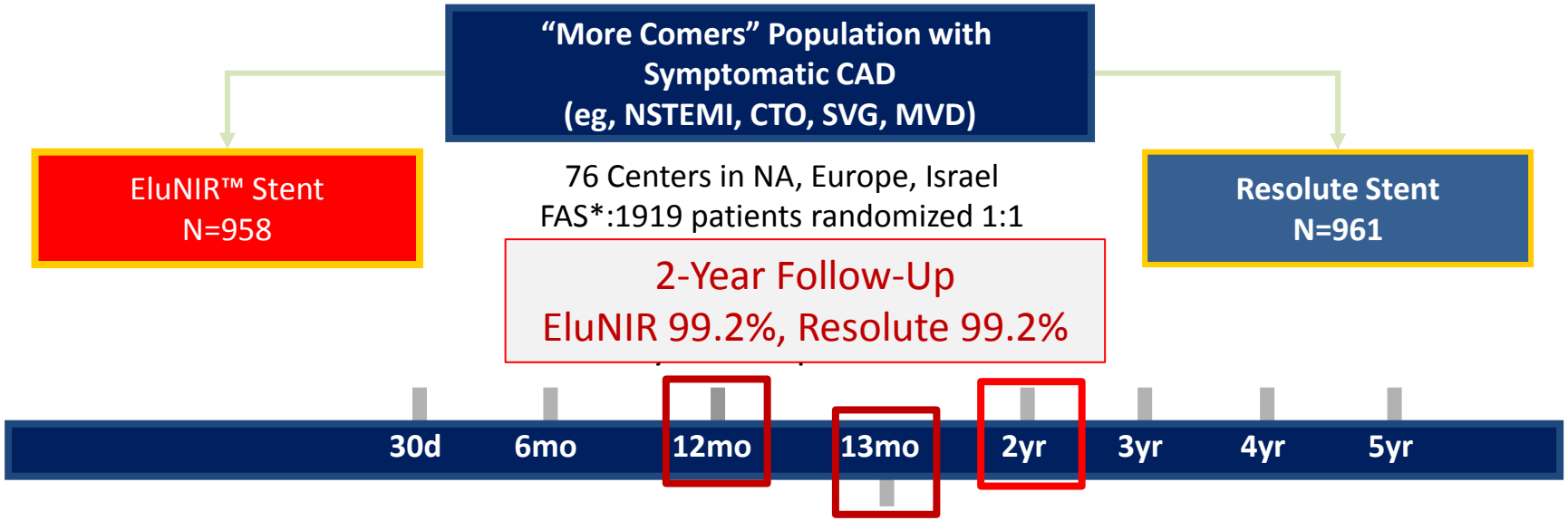
BIONICS Trial Design



Primary Endpoint:

- 12-month target lesion failure (TLF), composite of cardiac death, target vessel MI and ischemia driven TLR

Secondary Endpoints:

- 12-month MACE, TVF and individual component endpoints
- Definite/probable stent thrombosis
- Procedural success

*FAS= Full Analysis Set

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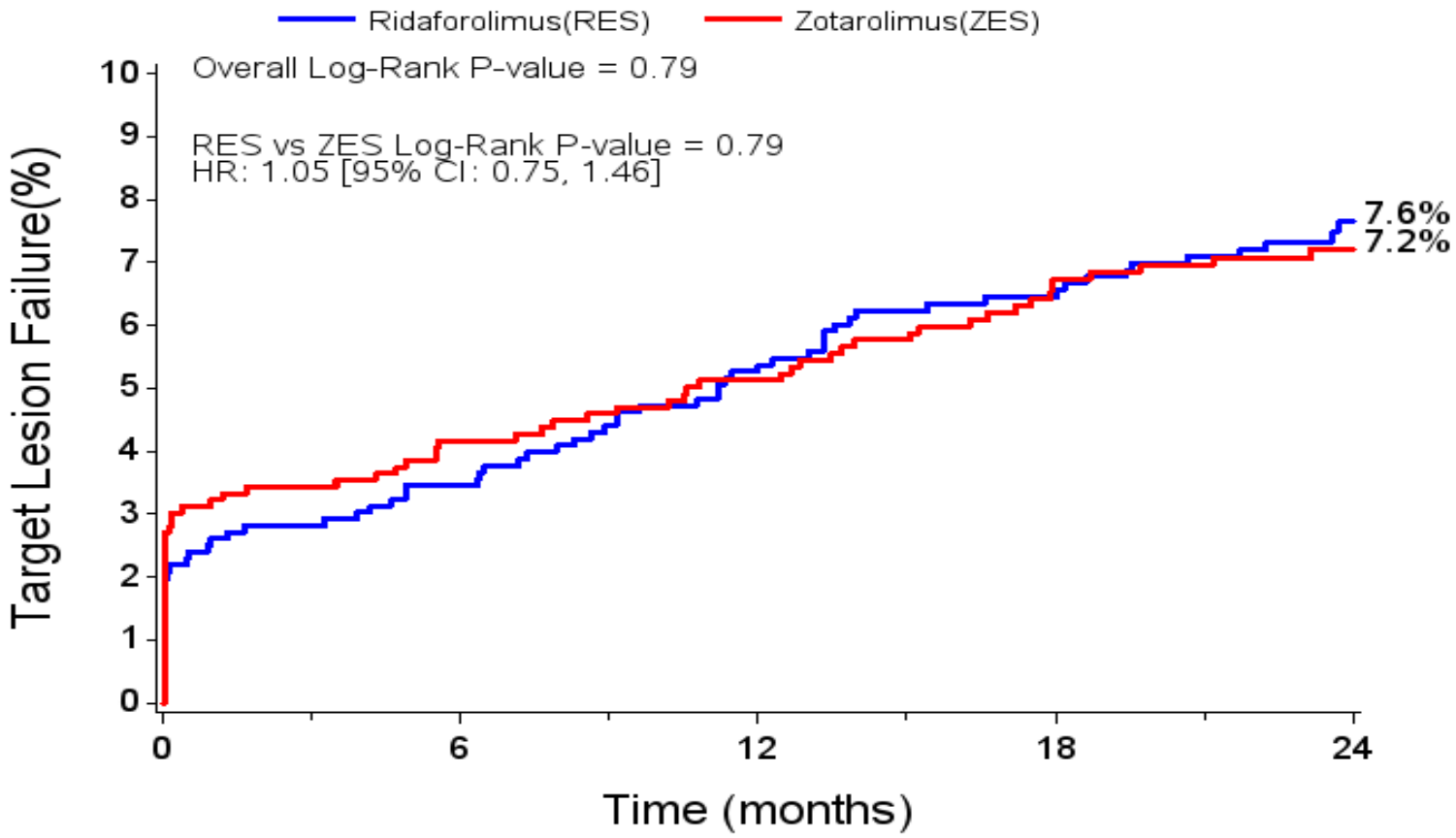
BIONICS
TLF to 24 Months



Number at risk:

Ridaforolimus	958	913	885	864	493
Zotarolimus	961	910	888	864	499

2 year clinical follow-up 99.2% in both groups

Kandzari et al. CRT 2018

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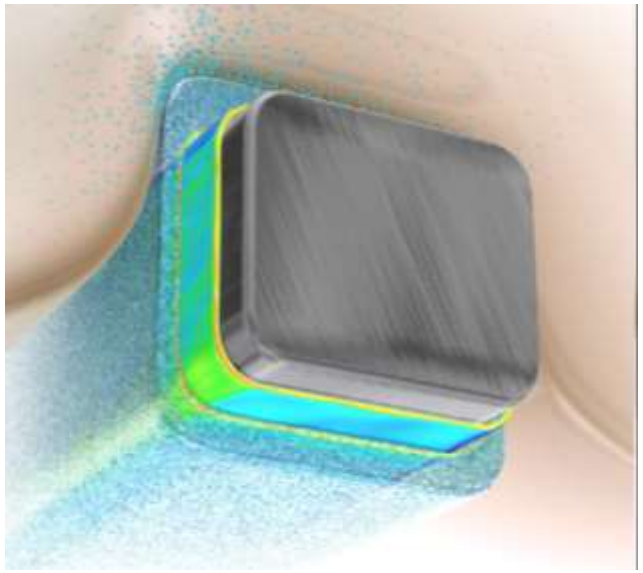
Orsiro Ultrathin Strut (BP SES) Stent System

Stent material	L-605 Cobalt-Chromium
Strut thickness	60 µm*
Polymer material	Poly-L-lactic acid (PLLA)
Polymer type	Bioresorbable, asymmetric circumferential thickness; scission begins immediately with 24 month complete degradation
Passive coating	Amorphous silicon carbide
Antiproliferative drug	Sirolimus (1.4 µg/mm^2), >80% eluted in first 90 days



*For 2.25mm to 3.0mm diameter stents, 80 µm for >3.0 mm diameter stents

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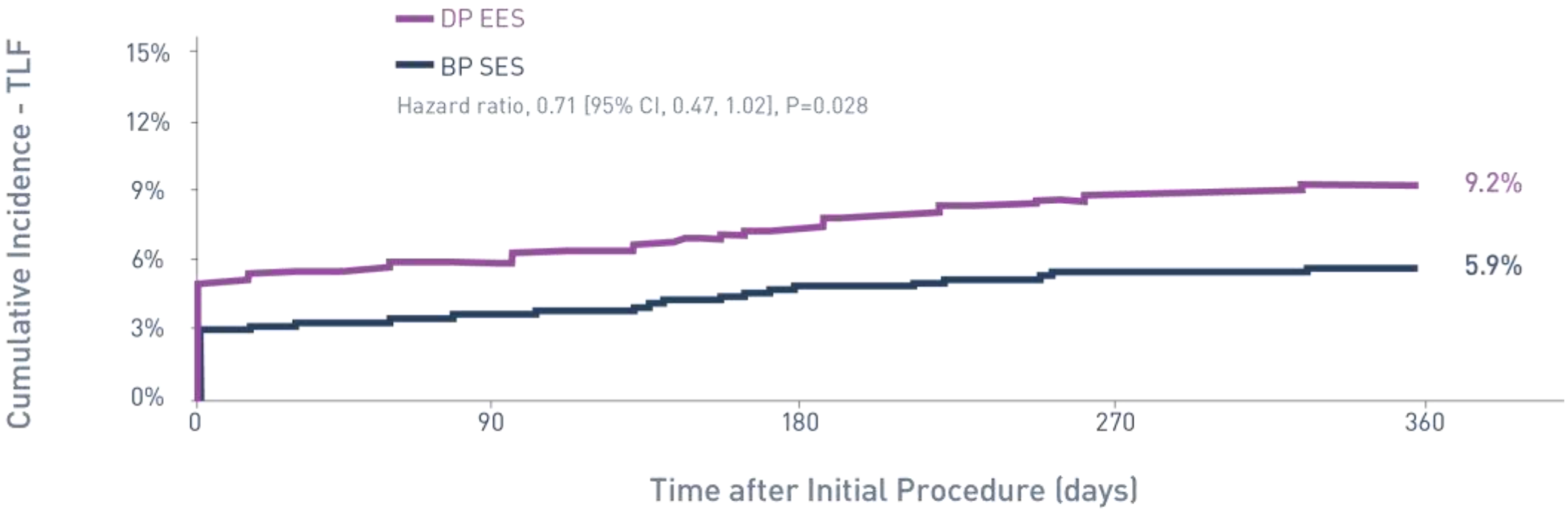
BIOFLOW V
Primary Endpoint: 12 Month Target Lesion Failure



No. at Risk					
DP EES	450	421	411	400	392
BP SES	884	848	828	814	792

Kandzari et al. Lancet 2017

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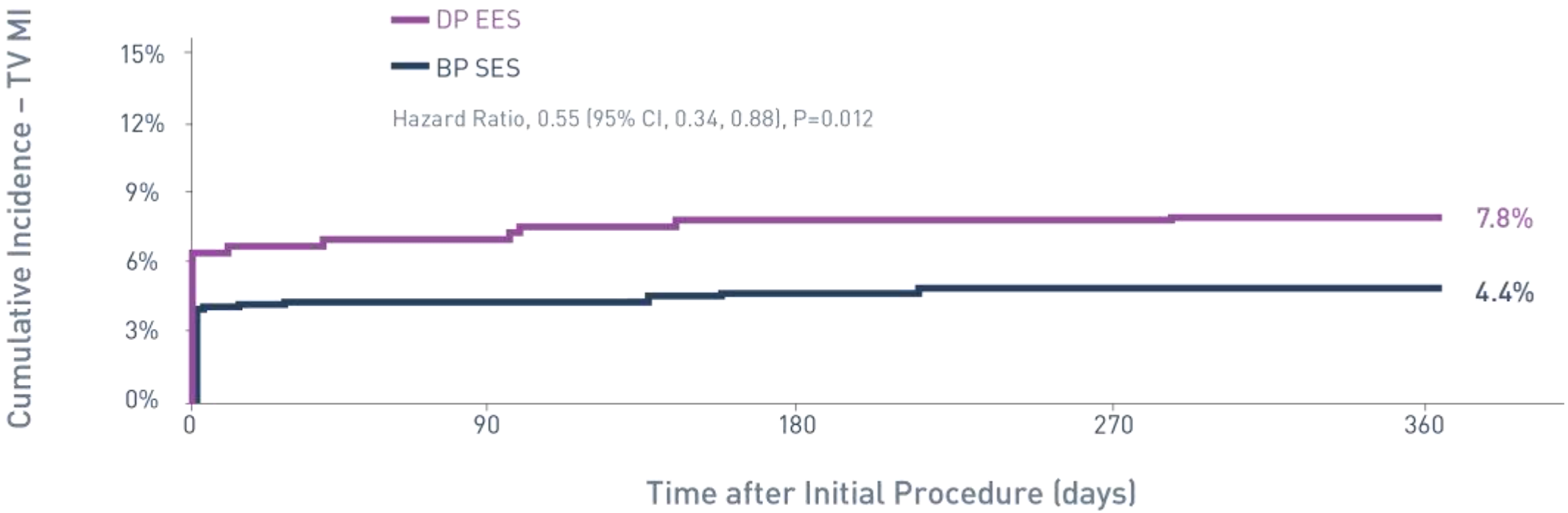
BIOFLOW V
12 Month Target Vessel-Related Myocardial Infarction



No. at Risk					
DP EES	450	421	411	400	392
BP SES	884	848	828	814	792

Kandzari et al. Lancet 2017

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BIOFLOW V
Pooled Bayesian Analysis: BIOFLOW V, II and IV Trials

	Orsiro BP SES (n=1466)	Xience DP EES (n=742)	Rate difference	Posterior probability	
Target lesion failure (Bayesian analysis)				Noninferiority margin 3.85%	Superiority (post-hoc)
12-Month Rate, posterior mean ± estimate of SD (%), 95% Credible Interval	6.3 ± 0.8 (4.9, 7.9)	8.9 ± 1.2 (6.7, 11.4)	-2.6 (-5.5, 0.1)	100.0%	96.9%

Kandzari et al. Lancet 2017

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Revisiting the Thin Strut Hypothesis (or Principle)

- Thinner stent struts produce less inflammation, vessel injury, neointimal proliferation and thrombus formation compared with thicker struts[1]

- Over 15 years of DES iteration, progression to thinner struts is associated with lower rates of target vessel MI

  - Stainless steel (132 µm to 140 µm) to chromium alloys (81 µm to 91 µm) translate to ~40% to ~80% reductions in both procedural and late-term target vessel MI[2]

- In BIOFLOW V, an ~20 µm difference between BP SES and DP EES is associated with 40% reduction in TV MI

[1]Kolandaivelu. Cirulation 2011; Soucy. EuroIntervention 2010; Kastrati. Circulation 2001; Pache. JACC 2003
[2]ENDEAVOR III; SPIRIT III; ENDEAVOR IV; ENDEAVOR Pooled Analysis; SPIRIT IV

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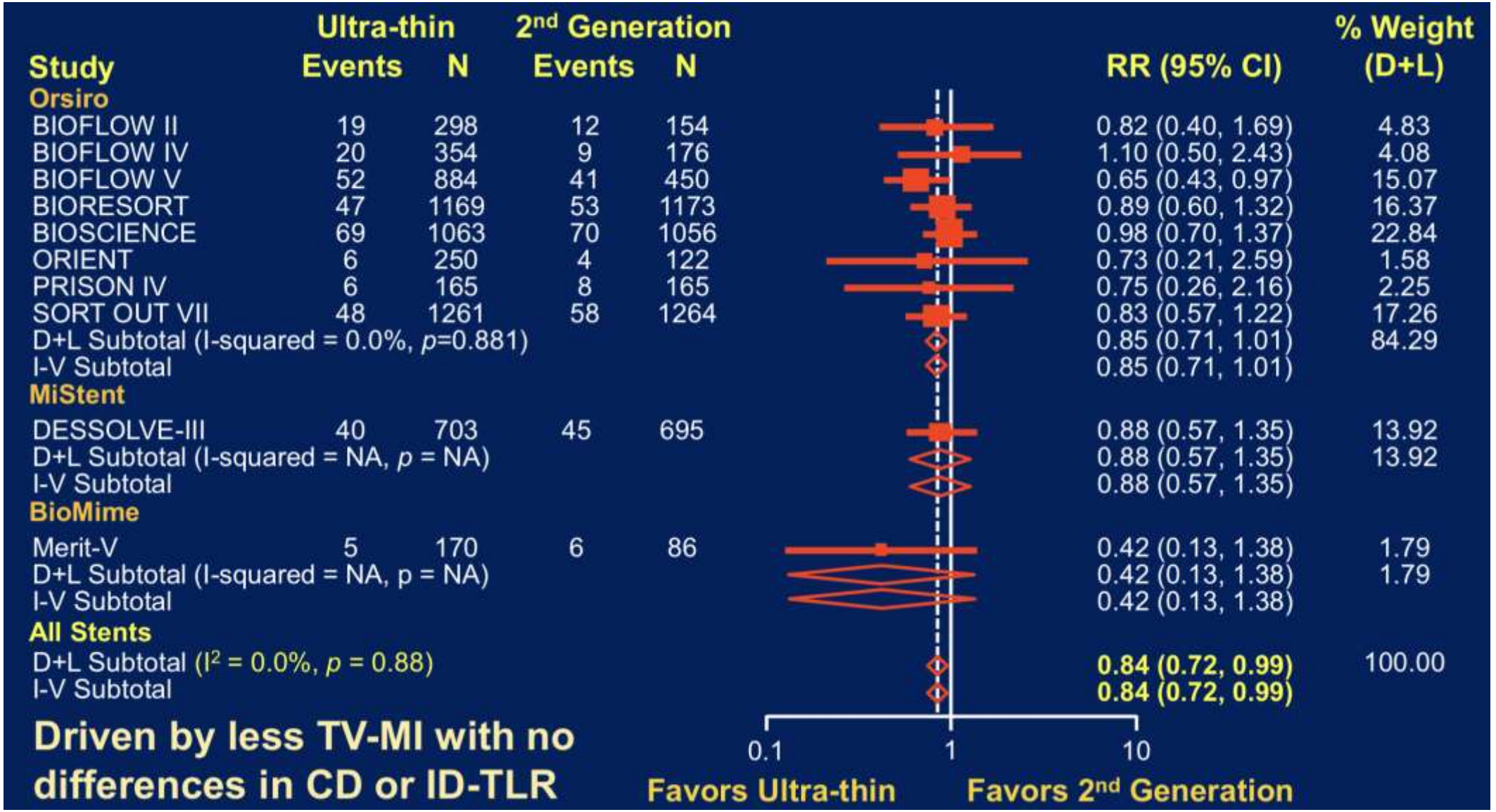
Ultra-thin (<70 μm) vs Thicker Strut 2nd Generation DES: 1-yr TLF

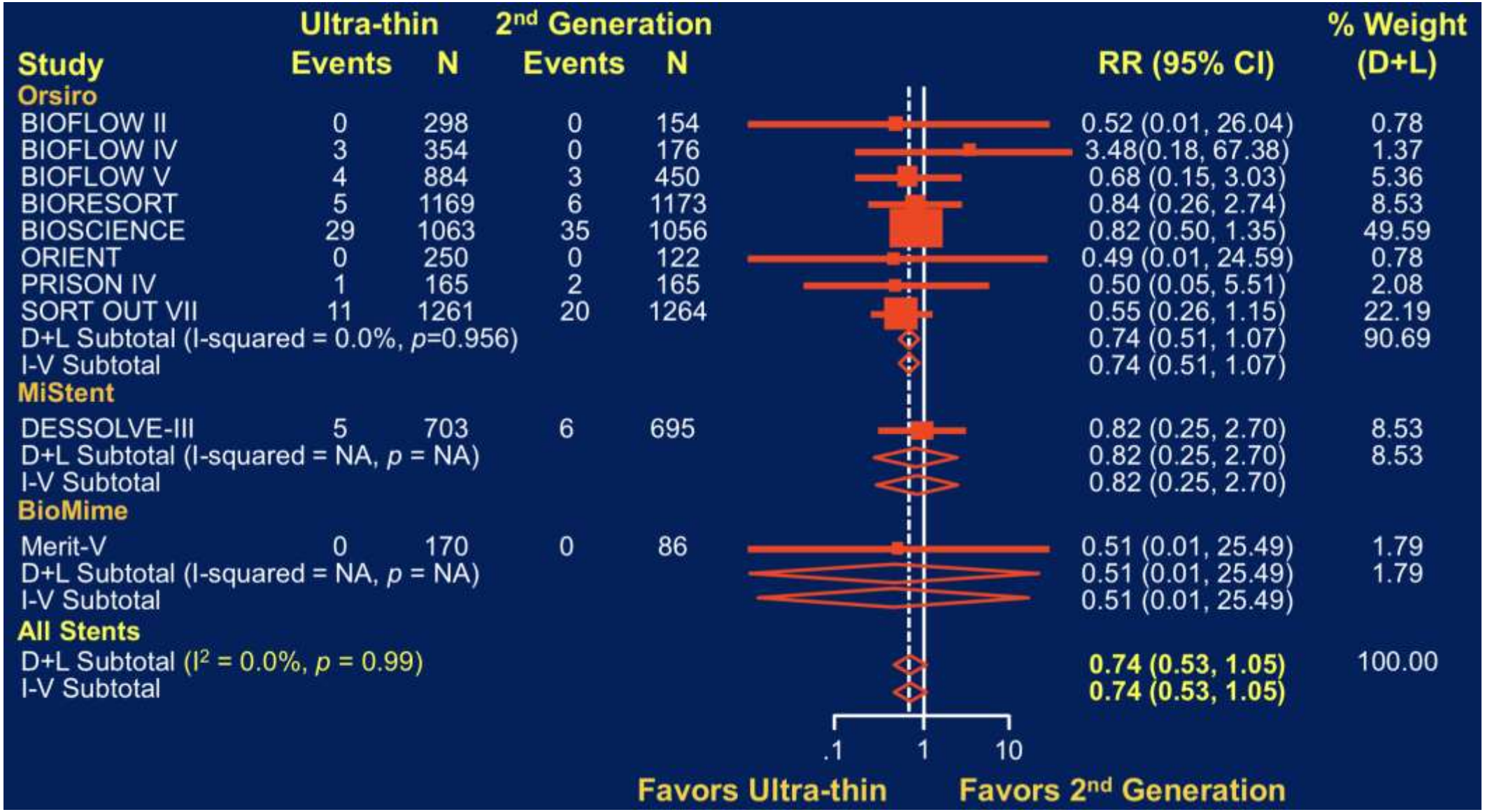
10 RCTs, 11,658 pts: Orsiro (60 μm), MiStent (64 μm), BioMime (65 μm)



Bangalore et al. Submitted

Ultra-thin (<70 μm) vs Thicker Strut 2nd Generation DES: 1-yr Def/Prob Stent Thrombosis

10 RCTs, 11,658 pts: Orsiro (60 μm), MiStent (64 μm), BioMime (65 μm)

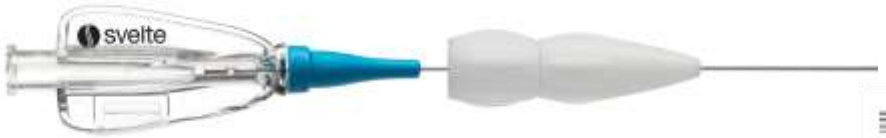


Bangalore et al. Submitted

SLENDER Integrated Delivery System (IDS) Designed to Facilitate TRI, Direct Stenting

Drug-Eluting Coronary Stent-on-a-Wire Integrated Delivery System (IDS)

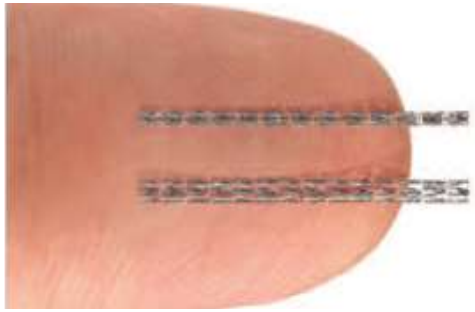
- Lowest profile DES system available, downsizes sheaths and catheters (0.047" ID* compatible)
  - Reduces the procedural steps, time and cost of PCI



0.031" crossing profile

Ultra-low Profile, Conformable Stent

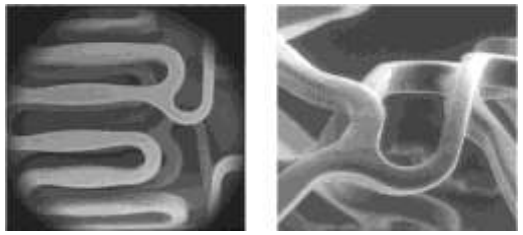
~½ the crimped cross-sectional profile of current DES*



*5F diagnostic catheter

Technology Designed for Direct Stenting

Low-compliant balloon material allows high-pressure inflation; bioresorbable amino acid drug coating (PEA; **DISCREET)**



Resorbs in 12 months

Asahi Wire Tip Technology

Asahi ACT ONE™ wire tip technology
World's leading guidewire brand

ASAHI TECHNOLOGY
Incorporates Asahi Wire Tip Technology

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OPTIMIZE International IDE

PRINCIPAL INVESTIGATOR
Dean Kereiakes, MD, USA
Sunil Rao, MD, USA

1630 Patients (815 Slender IDS / DIRECT Rx / 815 Xience or Promus)

150 patient angiographic, 60 patient IVUS sub-studies

1 & 6 month follow-up

12 month follow-up
TLF Primary Endpoint, NI margin 3.58%, α 0.025 (ITT)
in-stent LLL sub-study endpoint, NI margin 0.15mm, SD +/-0.32, α 0.05

2, 3, 4, 5 yr. follow-up

Study will include collection of data on direct stenting*, radial access and procedural efficiencies (independent economic analysis)

Clinical Sites:

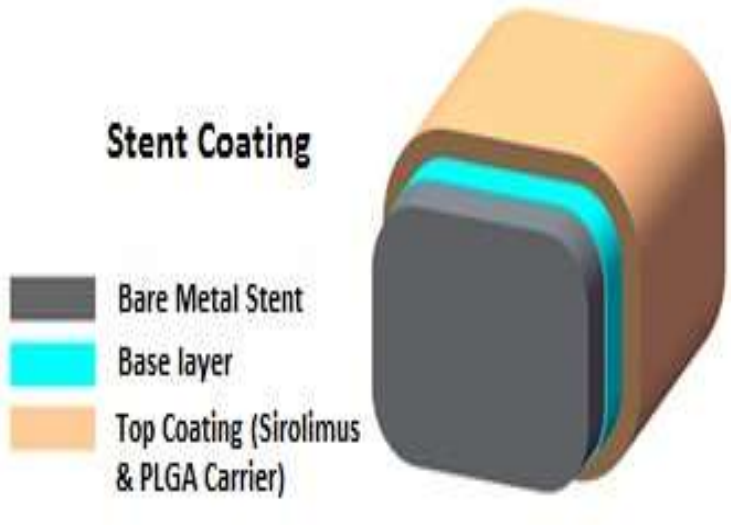
USA and Canada ≤ 90
Japan ≤ 10
EU ≤ 20

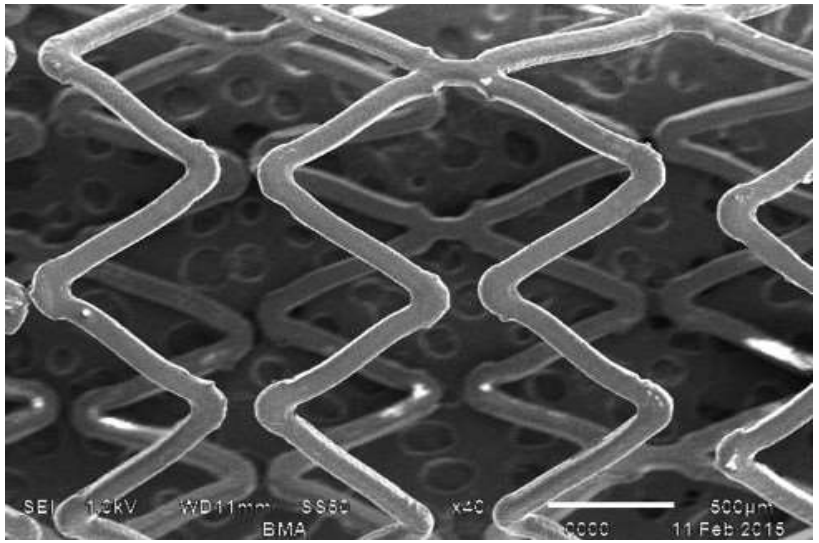
* randomization stratified by direct stent intent

CAUTION- Investigational Device. Not available for sale in the USA. SLENDER IDS is CE approved. warnings and instructions for use can be found in the product labeling supplied with each device.

BuMA Supreme DES Components

- Bare metal stent
  - A thin (**80 µm**) **CoCr stent** designed for deliverability and durability
- Base layer
  - A thin (100-200 nm) permanent poly n-butyl methacrylate (**PBMA**) coating **electro-grafted (eG) onto CoCr stent** to improve adhesion of the top coat
- Top coating
  - A poly lactic -co-glycolic acid (**PLGA**) biodegradable coating containing sirolimus (~1.2 µg/mm^2). The PLGA is **absorbed in ~6 weeks** with drug measurable in the artery for 150 days.





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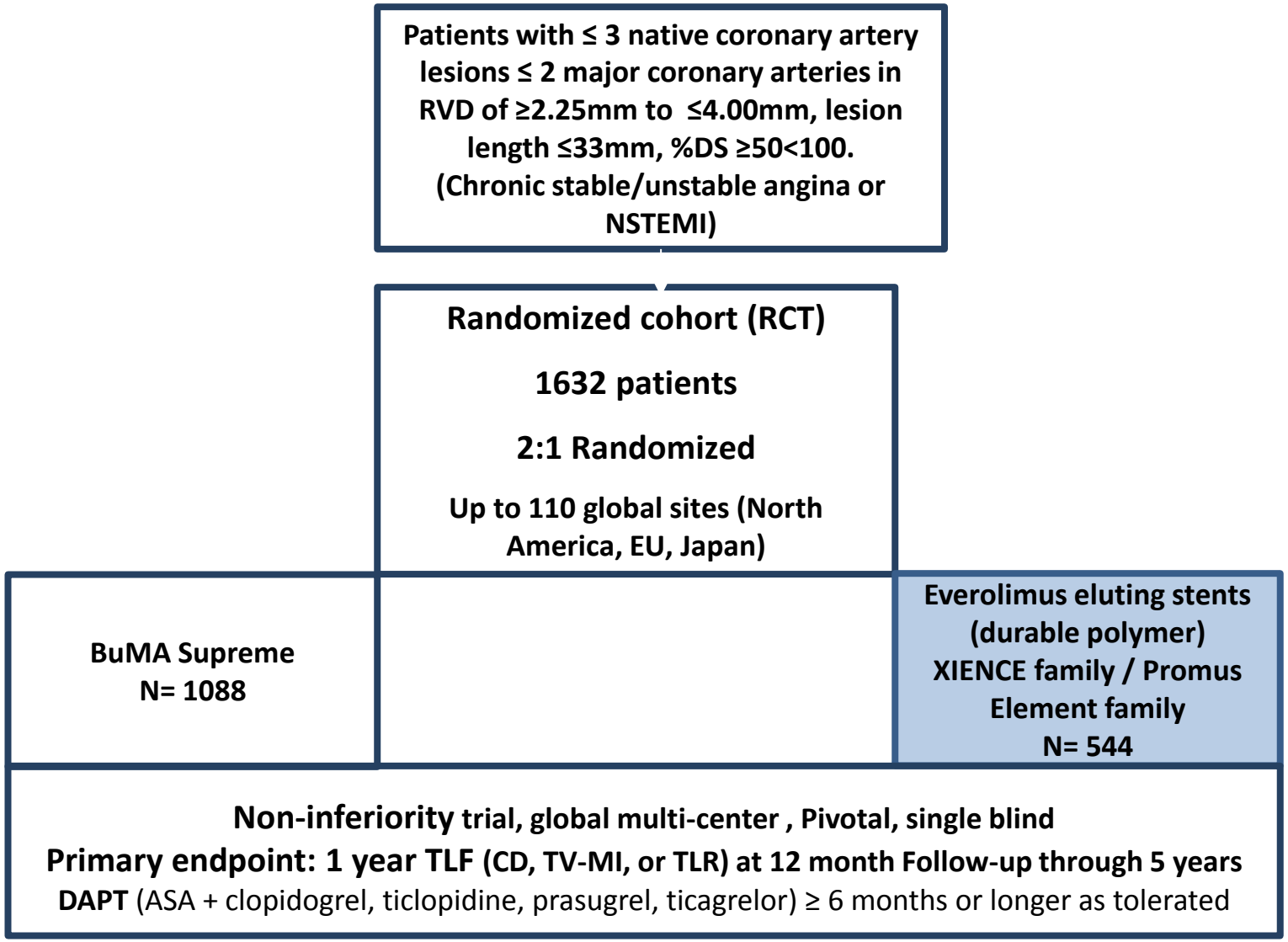
PIONEER III TRIAL DESIGN (IDE)



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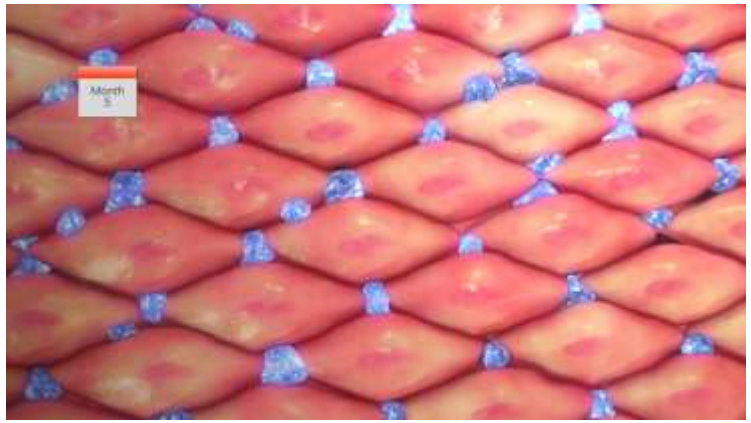
Crystalline Sirolimus with a Rapidly Absorbed Polymer Coating

MiStent Crystalline Sirolimus

- Unique to MiStent SES
- Micro-crystalline morphology
- Controlled and prolonged elution, as opposed to use of an amorphous, rapid-release form of the drug



MiStent Rapidly Absorbable Polymer

- Flows off the stent struts in 45 - 60 days
- Rapidly absorbed from tissue within 90 days
- Quickly eliminates source of inflammatory response

MiStent Thin-Strut Stent

- Cobalt-chromium
- Highly deliverable

(64 microns)

Carlyle, W., et al. J. Control Release. 2012

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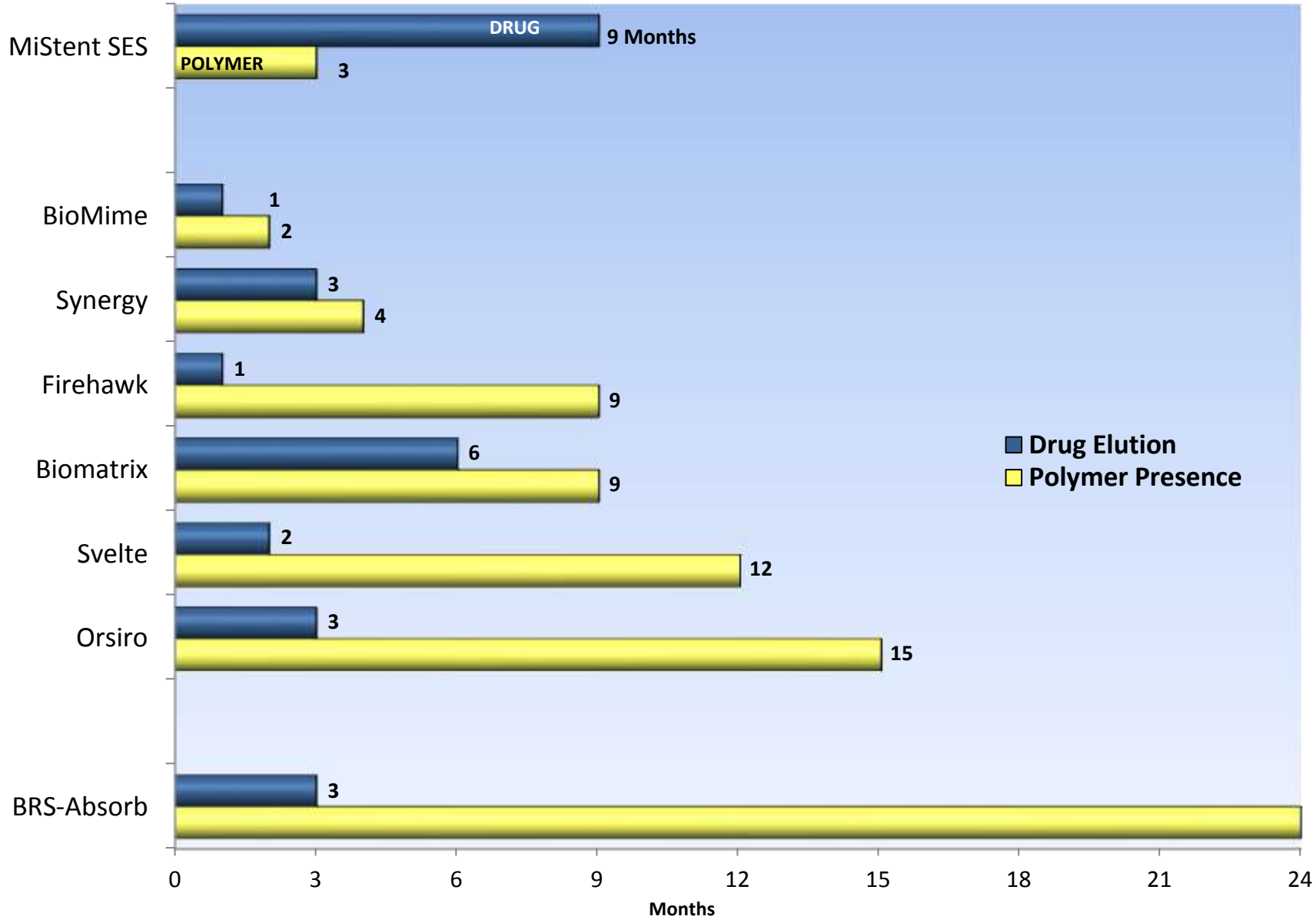
Bioresorbable Polymer DES

Differential Temporal Drug Delivery and Polymer Dissolution



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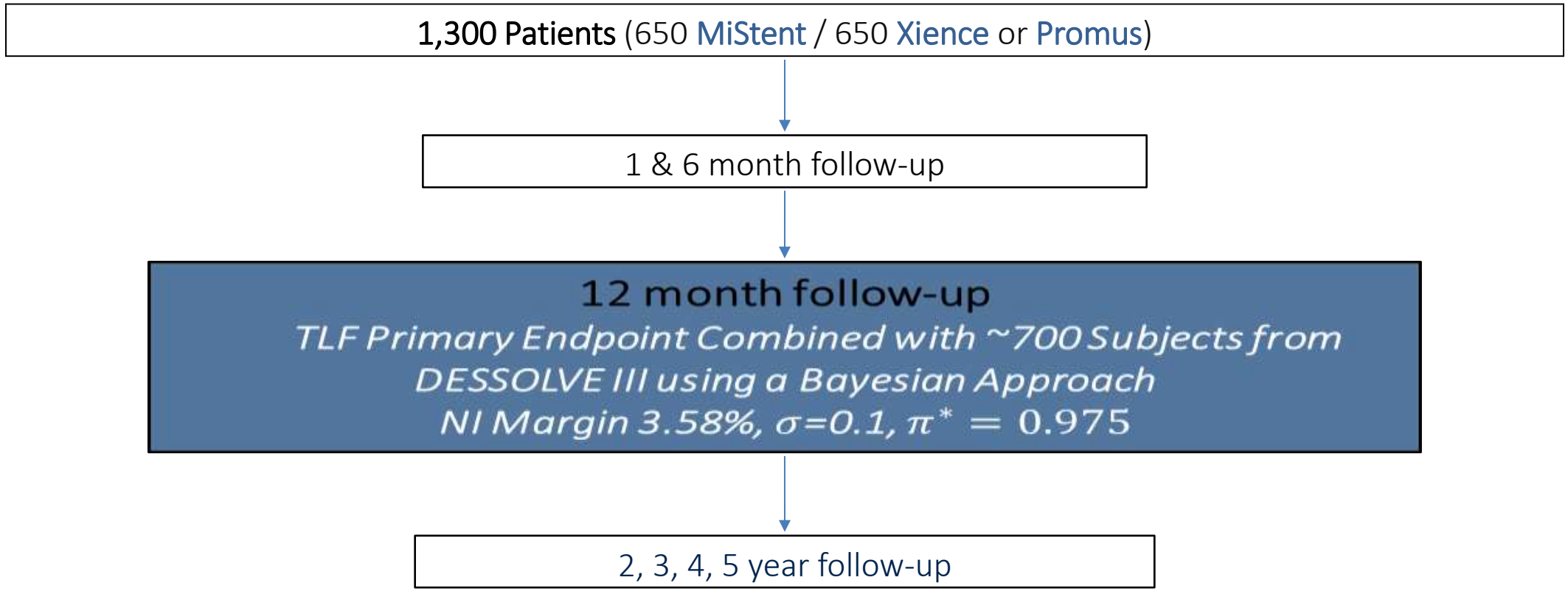
CRYSTAL International IDE

Co-PRINCIPAL INVESTIGATORS
Dean Kereiakes, MD, Cincinnati, OH (USA)
David Kandzari, MD, Atlanta, GA (USA)
Core Lab
Alexandra Lansky, MD, New Haven, CT (USA)



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Evolution of Interventional Cardiology

A Never Ending Work in Progress

- Evolution is inherent to interventional cardiology; an entrepreneurial spirit and passion for experimental research and evidence-based practice
- Until recently, the history and psychology of interventional cardiology has been consumed by anticipation of ‘what’s next’ and that the assumption of ‘what’s next’ is better
- We are realizing the best outcomes with PCI than ever before reported
- As newer DES are introduced, adoption will be driven more by intuition than scientific evidence as the opportunity to refine outcomes is increasingly difficult– *our patients deserve more than intuition*
- Opportunities remain to develop novel drug, polymer and stent delivery systems with selected attributes of each that confer incremental clinical and performance benefits above existing technologies– *Need to level set expectations regarding when, where and how differences will be observed*
- Introduction of new technologies enables us to address existing challenges, test strategy or a new advantage, and demonstrate value that informs dilemmas in existing practice

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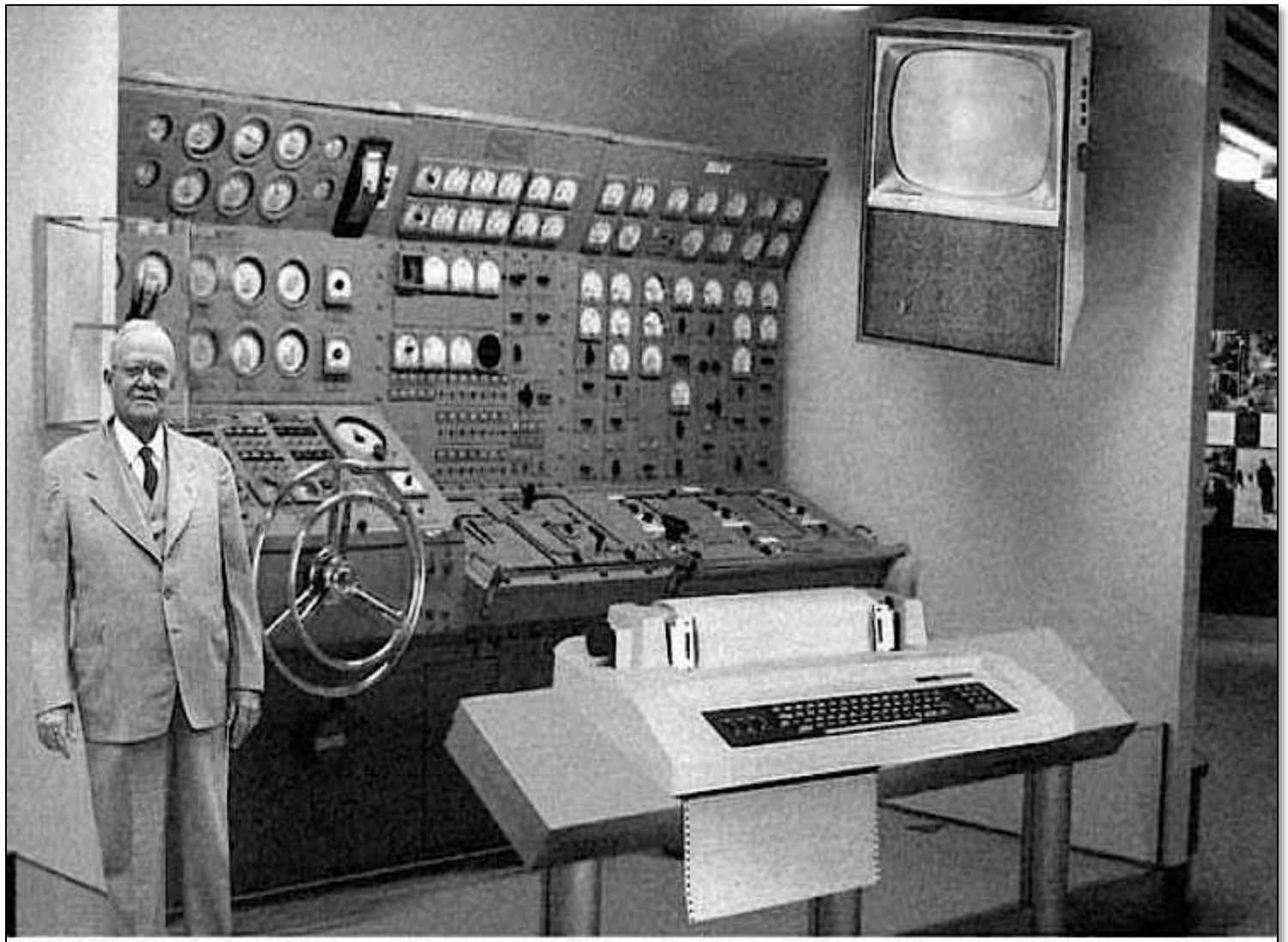

Scientists from the RAND Corporation have created this model to illustrate how a "home computer" could look like in the year 2004. However the needed technology will not be economically feasible for the average home. Also the scientists readily admit that the computer will require not yet invented technology to actually work, but 50 years from now scientific progress is expected to solve these problems. With teletype interface and the Fortran language, the computer will be easy to use.

Popular Mechanics, 1954

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