Randomized Trial of a Sirolimus Eluting Balloon versus Repeat Drug-Eluting Stenting or Balloon Angioplasty for Coronary In-stent Restenosis

SELUTION4ISR Clinical Trial

ClinicalTrials.gov ID NCT04280029

Donald E. Cutlip MD, on behalf of
the SELUTION4ISR investigators

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Disclosure of Relevant Financial Relationships

Within the prior 24 months, I, Donald E. Cutlip, have had a financial relationship with a company producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

Nature of Financial Relationship	Ineligible Company
Grant / Research Support	Cordis (MedAlliance), Corvia Medical
Consultant Fees / Honoraria	Boston Scientific

All Relevant Financial Relationships have been mitigated

Faculty disclosure information can be found on the app

Background

- **After drug-eluting stents, in-stent restenosis (ISR)** occurs in 4-8% of patients within one year and continues in over 1% of patients annually (>10% of PCI is ISR)
- Although **DES** has a Class 1A recommendation, many technologies have been explored to **avoid deploying multiple layers of stent**
- **Paclitaxel** drug-coated balloons (DCBs) have emerged as a new option for ISR treatment relative to POBA in clinical studies
- **Sirolimus** has a wider therapeutic window, but development had previously been delayed due to complexities of drug delivery and tissue uptake

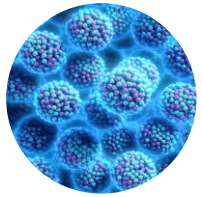
Study Device

SELUTION SLR Drug-Eluting Balloon

*Device not approved and available for sale in the US

MicroReservoirs

- ~4 µm spheres of **sirolimus** mixed with biodegradable polymer
- **Controlled release of sirolimus**



Proprietary Phospholipid Coating

- Phospholipid blend containing and protecting MicroReservoirs at 1 µg/mm^2 sirolimus dose
- **Enhanced drug transfer efficiency**

SELUTION SLR Drug-Eluting Balloon delivers sustained drug release that maintains therapeutic tissue concentration for 90 days[1]

[1] T Tanaka et al, Cardiovasc Revasc Med 2025: S1553-8389(25)00464-6

SELUTION4ISR Trial Design – Key Points

Goal: To demonstrate a DEB approach in ISR can achieve non-inferiority to standard of care (SOC) without the addition of another stent layer

Key Trial Design Considerations:

- Randomized, multi-center, single blind, **active control**, non-inferiority trial
- **Active control** designed as **standard of care** (SOC) in the United States based on NCDR[1] PCI registry data[1] indicating ~80% DES and 20% plain balloon angioplasty (BA)
- Operator required to select control treatment prior to randomization. BA group closed after 20% cap reached

[1]Moussa et al. J Am Coll Cardiol 2020;76:1521-31

Why SOC Control?

- Designed to mirror device use in NCDR registry report (2020) [1]
- Randomization to DES → concern with investigator reluctance; population limited to single layer ISR
- Randomization to plain balloon angioplasty → concern with random assignment to a known inferior treatment
- Operator selection of balloon angioplasty control limited to 20% and allowed comparison with a predominant repeat DES strategy

[1]Moussa et al. J Am Coll Cardiol 2020;76:1521-31

Study Organization

Principal Investigators

Donald E. Cutlip, MD
Beth Israel Deaconess Medical Center, Boston, MA

Roxana Mehran, MD
Icahn School of Medicine at Mount Sinai, New York, NY

Steering Committee

Chair: Ron Waksman, MD
MedStar Washington Hospital, Washington, D.C.

Donald E. Cutlip, MD
Roxana Mehran, MD
George Adams, MD, (CMO, Cordis)

Angiography Core Laboratory

Serge Korjian, MD
Baim Institute, Boston, MA

OCT Core Laboratory

Eric Osborn, MD, PhD.
Baim Institute, Boston, MA

DSMB Chair

Andreas Baumbach, MD
St. Bartholomew's Hospital, London, England

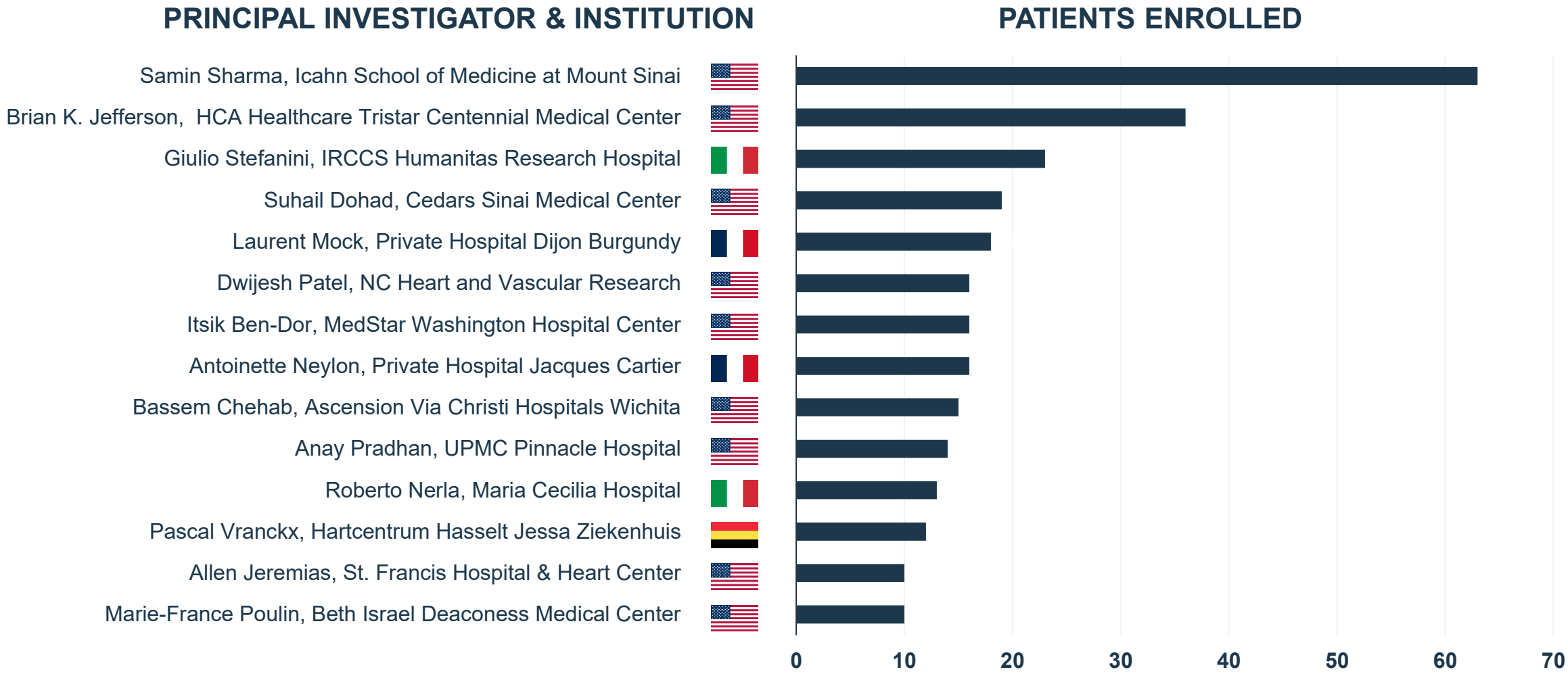
CEC Chair

Hector M Garcia-Garcia, MD
MedStar Washington Hospital, Washington, D.C.

Funding and Study Sponsor

Cordis, through its affiliate, M.A. MedAlliance SA

SELUTION4ISR Top Enrollers



Key Inclusion and Exclusion Criteria

Key Inclusion Criteria

- ✓ Age ≥ 18 years
- ✓ **Stable or unstable angina, functional testing demonstrating ischemia, or stabilized non-ST elevation MI**
- ✓ Eligible for DAPT
- ✓ >1 year life expectancy
- ✓ Single target lesion within native coronary artery
- ✓ **Target lesion within prior BMS or DES and not >5 mm from proximal or distal edge**
- ✓ Diameter stenosis >50 and <100%
- ✓ Lesion length ≤ 26mm; RVD ≥ 2.0 and ≤ 4.5 mm

Key Exclusion Criteria

- × STEMI within 30 days
- × Bifurcation requiring side branch treatment
- × **>2 layers of previous stent**
- × Total occlusion or thrombus present
- × **>30% diameter stenosis or dissection > NHLBI Type C after pretreatment**

Randomization and Study Procedure

Pre Study Procedure

All patients received:

- ASA ≥ 150 mg pre-procedure
- P2Y12 inhibitor pre or within 1 hour post

IVUS or OCT required pre-treatment

Pre-treatment with any approved device for residual stenosis <30%

Operator selection of DES or BA control pre-randomization – limit of 20% BA

Randomization stratified by: center, BMS/DES ISR, and 1 vs. 2 layers prior stent

Study Procedure

SELUTION DEB

- Balloon inflated (nominal) for goal 60 seconds and minimum 30 seconds
- **No additional PCI or intracoronary imaging**
- DAPT 1 month

DES

- Standard practice
- **Post-dilation and intracoronary imaging encouraged to optimize result**
- DAPT 6 months*

Balloon Angioplasty

- Additional BA if required for optimal result
- DAPT 1 month

*DAPT <6 months if high bleeding risk; P2Y12 monotherapy if required oral anticoagulation

Primary Endpoint and Statistical Analysis

Primary Endpoint

- Target Lesion Failure (cardiac death, target vessel MI*, clinically driven TLR)

Non-inferiority (*primary analysis in per protocol population)*

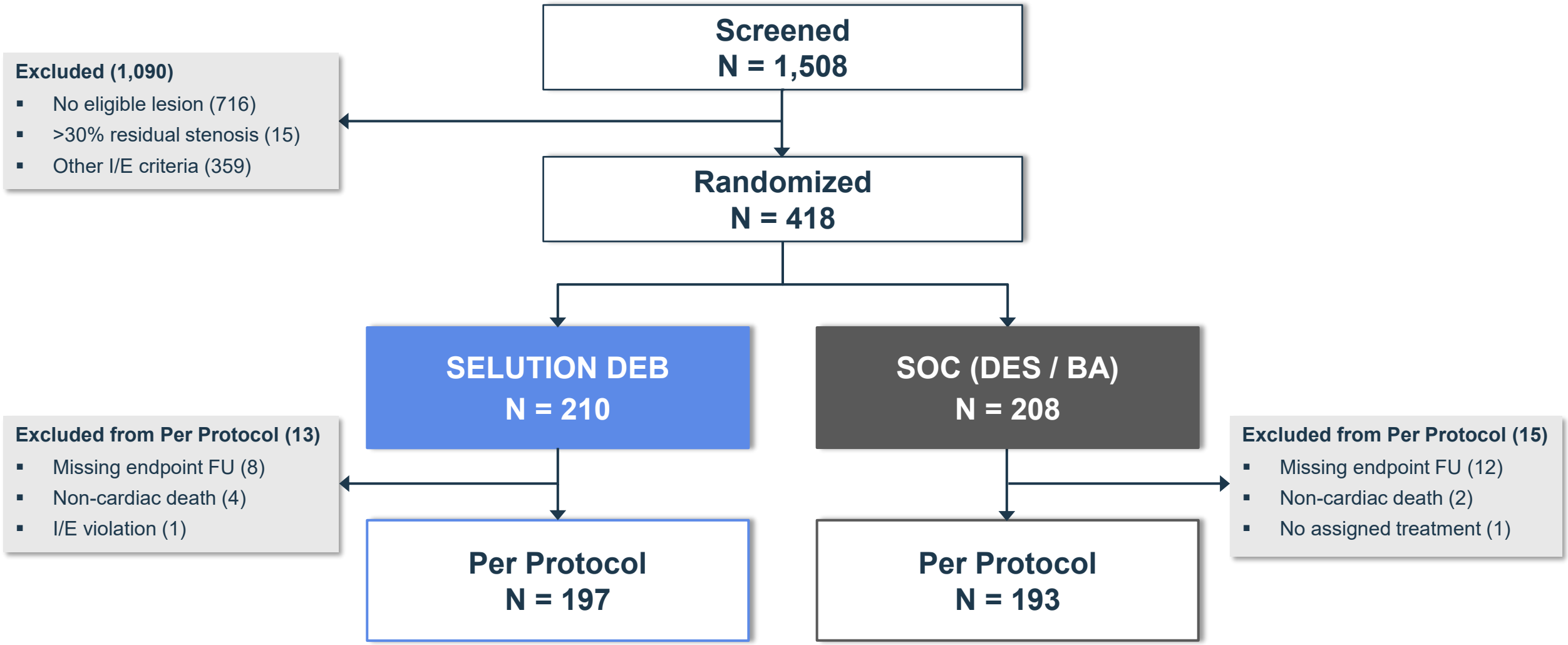
- Non-inferiority of proportions analyzed by **non-informative Bayesian method** requiring posterior probability of **97.5%** (~one-sided alpha 0.025); **Non-inferiority margin = 10%**
- Assumed event rate 12% per group; 5% loss to FU
- 84% power, sample size = 418 patients

Analysis repeated *in intention-to-treat population*

- Including analyses adjusting for missing data (time-to-event, multiple imputation, and tipping point)

***Peri-procedural by SCAI and post-procedure by 4th UDMI**

Study Flow – Consort Diagram



Baseline Clinical Characteristics (ITT)

Characteristic	SELUTION DEB N = 210	SOC N = 208
Age (years, median, IQR)	68 (63-75)	71 (63-76)
Female (N, %)	39 (19%)	55 (26%)
Diabetes (N, %)	90 (43%)	89 (43%)
Hypertension (N, %)	195 (93%)	193 (93%)
Hyperlipidemia (N, %)	190 (90%)	186 (89%)
Prior MI (N, %)	104 (50%)	101 (49%)
Current smoker (N, %)	33 (16%)	30 (14%)

Baseline Lesion Characteristics (ITT)

Characteristic	SELUTION DEB N = 210	SOC N = 208
Number of prior stents at target lesion		
One - N (%)	**167 (80%)**	**168 (81%)**
Two - N (%)	**43 (20%)**	**40 (19%)**
Prior DES at target lesion	185 (88%)	192 (92%)
Target lesion location - N (%)		
Left anterior descending	83 (40%)	80 (39%)
Circumflex	53 (25%)	47 (23%)
Right coronary artery	73 (35%)	74 (36%)
Restenosis Pattern - N (%)		
Focal	**78 (39%)**	**81 (43%)**
Diffuse	**116 (58%)**	**101 (53%)**
Proliferative	**5 (3%)**	**8 (4%)**

Baseline Quantitative Angiography (ITT)

Characteristic	SELUTION DEB N = 210	SOC N = 208
Lesion length⁺ (mm)	**12.3 ± 6.0**	**11.9 ± 5.6**
Reference vessel diameter⁺ (mm)	2.51 ± 0.50	2.55 ± 0.56
Minimum lumen diameter⁺ (mm)	0.87 ± 0.33	0.88 ± 0.36
Percent diameter stenosis⁺ (%)	**65.34 ± 12.02**	**65.49 ± 11.14**

⁺Core lab reported

Procedural Angiographic Results (ITT)

PRE RANDOMIZED TREATMENT

Characteristic	SELUTION DEB N = 210	SOC N = 208
Intravascular Imaging – N (%)	**206 (98%)**	**202 (97%)**
Pre-treatment device - N (%)		
Plain balloon angioplasty	184 (88%)	176 (85%)
Cutting Balloon	**58 (28%)**	**70 (34%)**
Scoring Balloon	**33 (16%)**	**39 (19%)**
Maximum device length (mm)	13.83 ± 4.71	13.22 ± 4.09
Maximum balloon diameter (mm)	3.12 ± 0.56	3.09 ± 0.66
Maximum inflation pressure (ATM)	**19.04 ± 6.41**	**19.37 ± 8.34**
Minimum lumen diameter⁺ (mm)	1.98 ± 0.44	1.94 ± 0.51
Percent diameter stenosis⁺ (%)	23.25 ± 12.36	25.01 ± 13.98

⁺Core lab reported

Procedural Angiographic Results (ITT)

POST STUDY DEVICE RESULTS

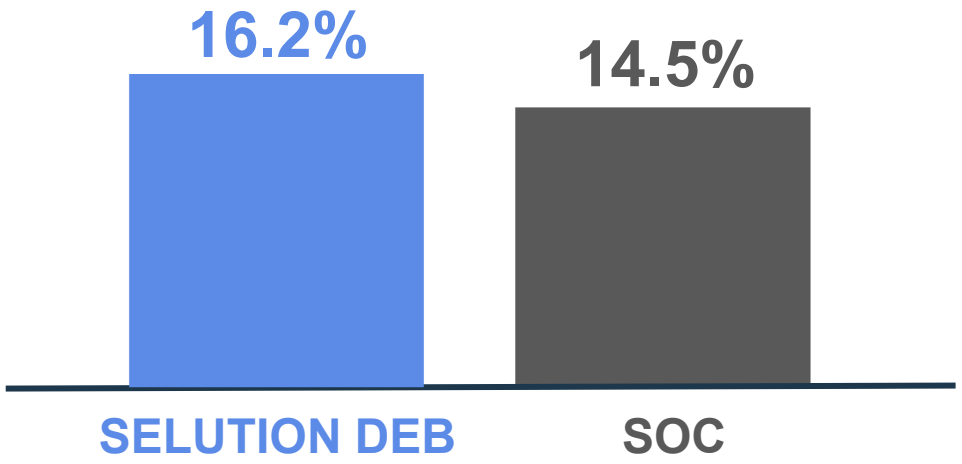
Characteristic	SELUTION DEB N = 210	SOC N = 208
Maximum device length (mm)	**21.5 ± 6.0**	**19.2 ± 7.5***
Maximum balloon diameter (mm)	3.2 ± 0.5	3.3 ± 0.5
Maximum inflation pressure (ATM)	**10.2 ± 3.7**	**16.1 ± 5.6***
Minimum lumen diameter[+] (mm)	**2.22 ± 0.44**	**2.47 ± 0.52***
Percent diameter stenosis[+] (%)	**16.74 ± 9.48**	**11.58 ± 9.75***
Procedure time (minutes)	54.2 ± 23.6	59.5 ± 31.0

[+]Core lab reported

*$p<0.05$

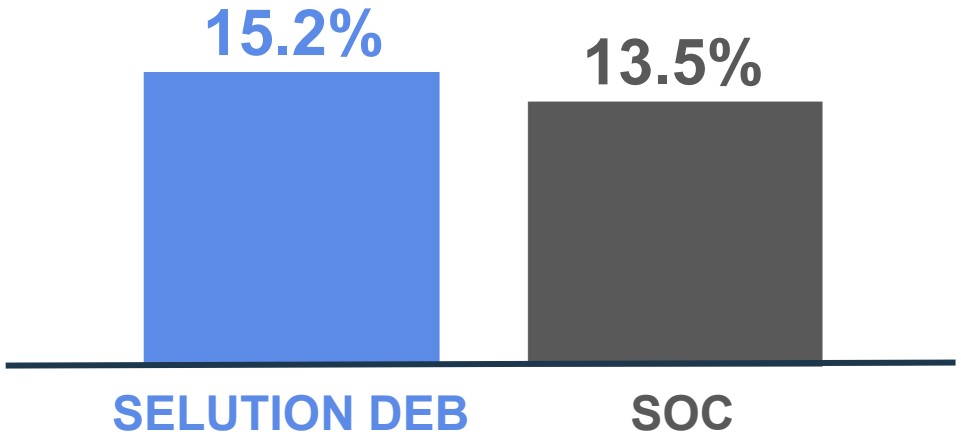
Primary Endpoint Results: TLF at 1-Year

Per Protocol (PP)



- Difference = 1.7%
- 95% Credible Interval (-5.5% – 8.9%)
- Posterior Probability for non-inferiority 98.8%

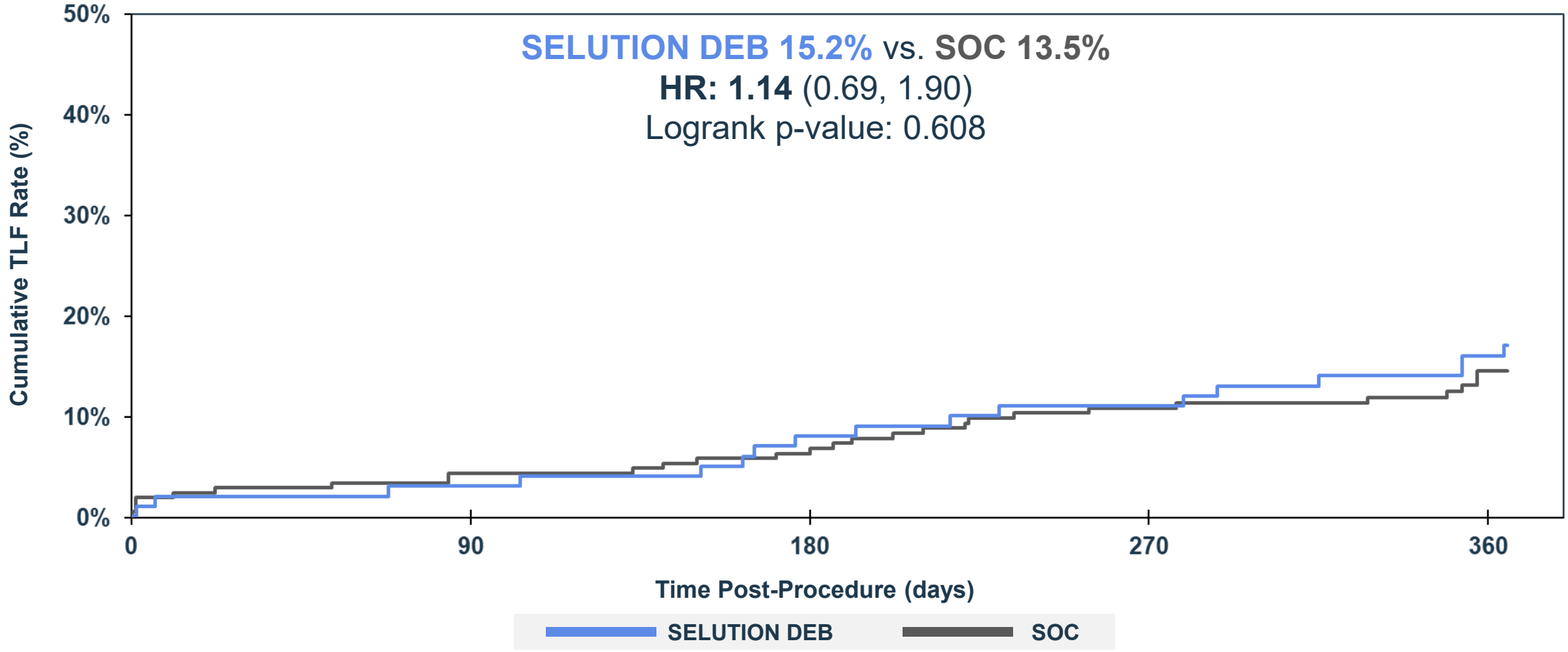
Intention to Treat (ITT)



- Difference = 1.8%
- 95% Credible Interval (-4.9% – 8.5%)
- Posterior Probability for non-inferiority 99.18%

SELUTION DEB is non-inferior to SOC, including ~80% DES

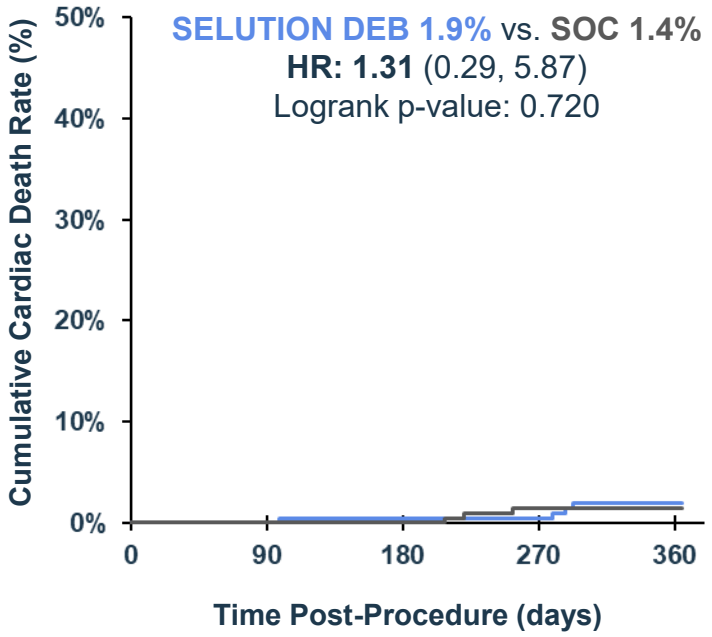
Cumulative Incidence: TLF (ITT)



# at risk					
SELUTION DEB	210	201	187	177	101
SOC	208	197	190	175	109

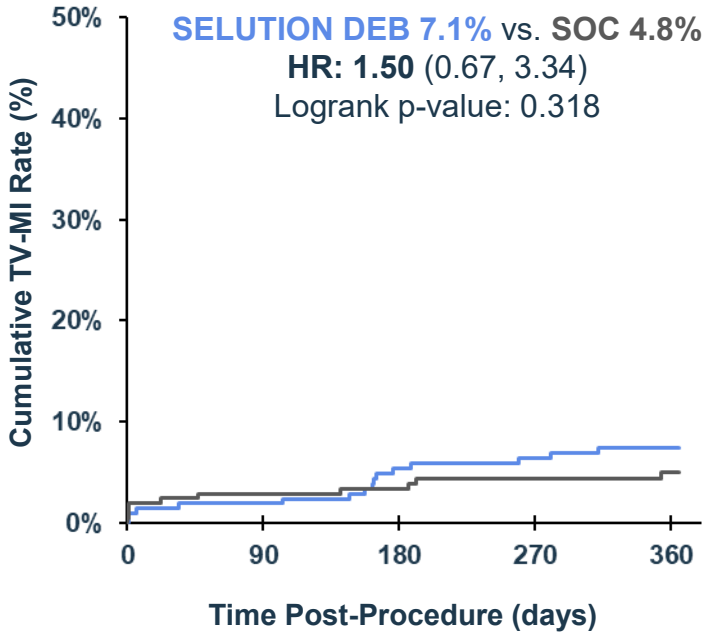
Cardiac Death, TV-MI, CD-TLR (ITT)

Cardiac Death



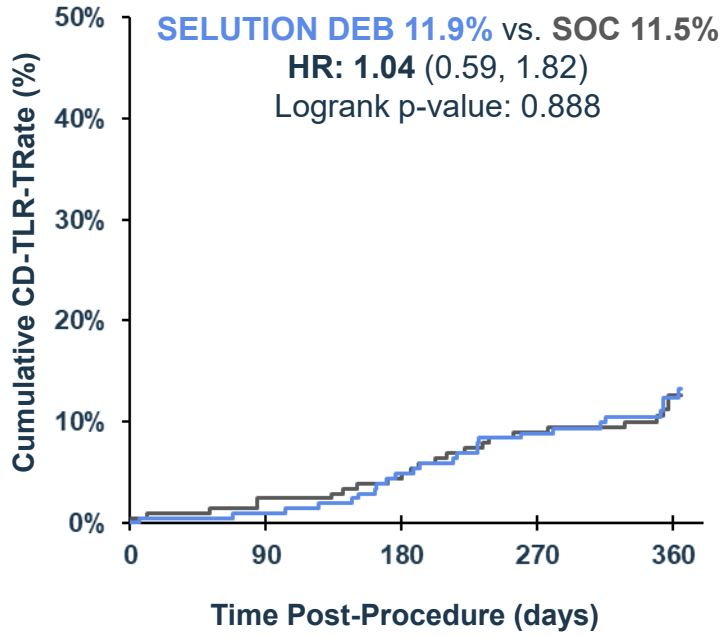
# at risk					
SELUTION DEB	210	207	202	199	122
SOC	208	206	203	194	127

TV-MI



SELUTION DEB	210	203	191	186	113
SOC	208	200	196	186	120

CD-TLR



SELUTION DEB	210	205	192	181	104
SOC	208	201	194	178	112

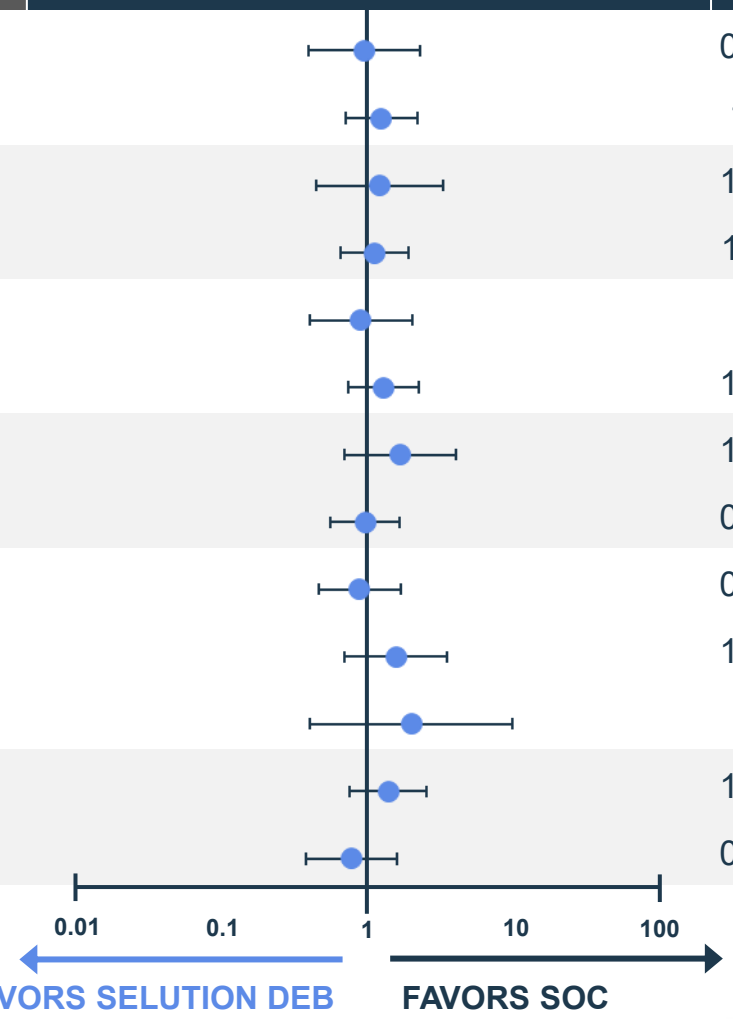
SELUTION DEB SOC

Secondary and Safety Endpoints (ITT)

Endpoint	SELUTION DEB N = 210	SOC N = 208
All-Cause Mortality, N (%)	9 (4%)	5 (2%)
Cardiac Death, N (%)	4 (2%)	3 (1%)
All Myocardial Infarction, N (%)	17 (8%)	13 (6%)
Target vessel MI, N (%)	15 (7%)	10 (5%)
Peri-procedural, N (%)	2 (1%)	4 (2%)
Post-procedure, N (%)	13 (6%)	7 (3%)
All TLR, N (%)	27 (13%)	26 (13%)
Clinically-driven TLR, N (%)	25 (12%)	24 (12%)
Stent (lesion) thrombosis N (%)	4 (2%)	4 (2%)
Definite, N (%)	2 (1%)	3 (1%)
Probable, N (%)	2 (1%)	1 (1%)
Bleeding (BARC 2-5), N (%)	16 (8%)	21 (10%)

Subgroup Analysis – Forest Plot (ITT)

Subgroup		SELUTION DEB	SOC	Relative Risk Difference	RR (95% CI)	Interaction p-value
Age	>75	7/44 (16)	10/60 (17)		0.95 (0.39 – 2.31)	**0.632**
	<= 75	25/166 (15)	18/148 (12)		1.24 (0.7 – 2.18)	
Sex	Female	6/39 (15)	7/55 (13)		1.21 (0.44 – 3.32)	**0.882**
	Male	26/171 (15)	21/153 (14)		1.11 (0.65 – 1.89)	
Medical History of Diabetes	No Diabetes	10/120 (8)	11/119(9)		0.9 (0.4 – 2.04)	**0.464**
	Diabetes	22/90 (24)	17/89 (19)		1.28 (0.73 – 2.24)	
Reference Vessel Diameter	> 2.75	11/67 (16)	7/71 (10)		1.67 (0.69 – 4.04)	**0.302**
	<= 2.75	21/143 (15)	21/137 (15)		0.96 (0.55 – 1.67)	
Lesion Length	< 10mm	14/93 (15)	17/99 (17)		0.88 (0.46 – 1.68)	**0.43**
	10 - 20mm	14/92 (15)	8/82 (10)		1.56 (0.69 – 3.53)	
	> 20 mm	4/24 (17)	2/24 (8)		2 (0.4 – 9.91)	
Number of Stent Layers	One	22/167 (13)	16/168 (10)		1.38 (0.75 – 2.54)	**0.242**
	Two	10/43 (23)	12/40 (30)		0.78 (0.38 – 1.59)	



TLF by Selected Randomization

	Randomized to DES		Randomized to BA	
	SELUTION DEB N = 163	DES N = 154	SELUTION DEB N = 34	BA N = 39
Target Lesion Failure, N (%)	25 (15.3%)	11 (7.1%)	7 (20.6%)	17 (43.6%)

Limitations

- The 10% non-inferiority margin is high relative to the event rate and must be interpreted in context of clinical benefit (avoiding an additional stent layer)
- Current results and interpretation are limited to 1 year follow-up and differences may emerge over time
- Patients with more than 2 layers of previous stents were not included
- Blended control group reflecting a contemporary standard of care in the United States

Conclusions

- SELUTION DEB is the first and only DEB to demonstrate non-inferiority against a SOC (including 80% DES) for the treatment of ISR
- SELUTION DEB is a safe and effective alternative to SOC (~80% DES and 20% BA) ISR treatment avoiding additional layers of stent
- The role of DEB versus DES for lifetime management of ISR will be studied through long-term follow-up