BIONICS Trial

BioNIR Ridaforolimus Eluting Coronary Stent System In Coronary Stenosis Trial

David E. Kandzari, MD

on behalf of the

BIONICS investigators

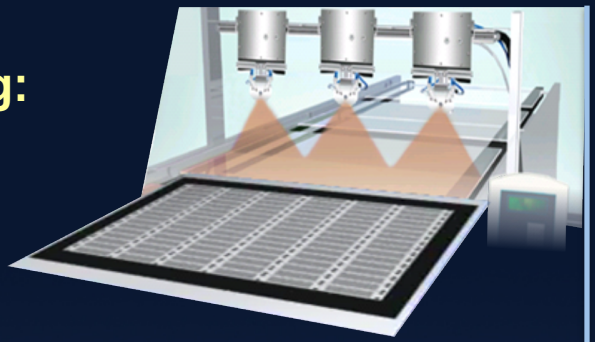
Disclosure

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

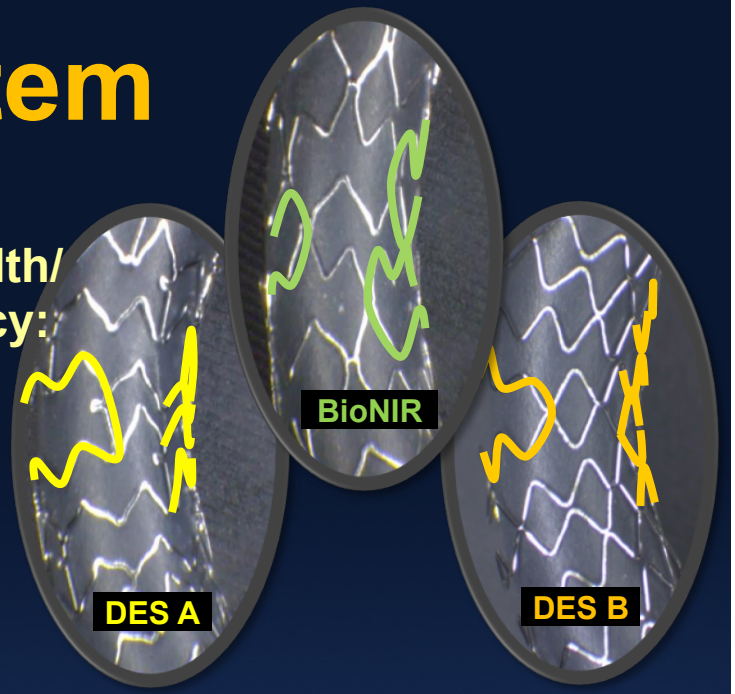
Affiliation/Financial Relationship	Company
Grant/Research Support	Abbott Vascular, Boston Scientific, Medtronic CardioVascular, Biotronik, St. Jude Medical/Thoratec, Ablative Solutions
Consulting Fees/Honoraria	Boston Scientific Corporation, Medtronic CardioVascular, Micell, St. Jude Medical
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

BioNIR System

Flat manufacturing: Quality & cost efficiency

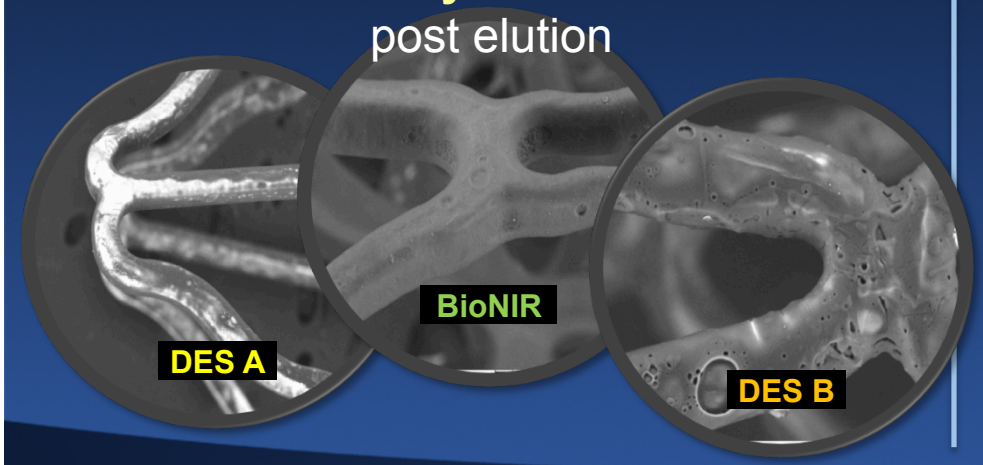


Variable strut width/ frequency: Uniform dosing

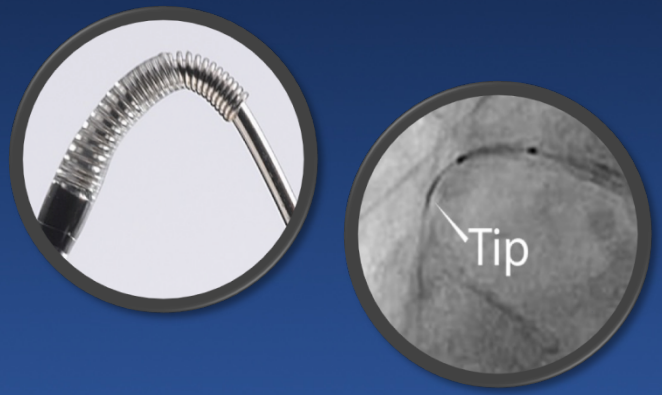


- *80µm CoCr Wizecell design*
- *Ridaforolimus high therapeutic index drug*

Elastomeric Polymer: Remains intact post elution



Spring tip: Pushable & visible



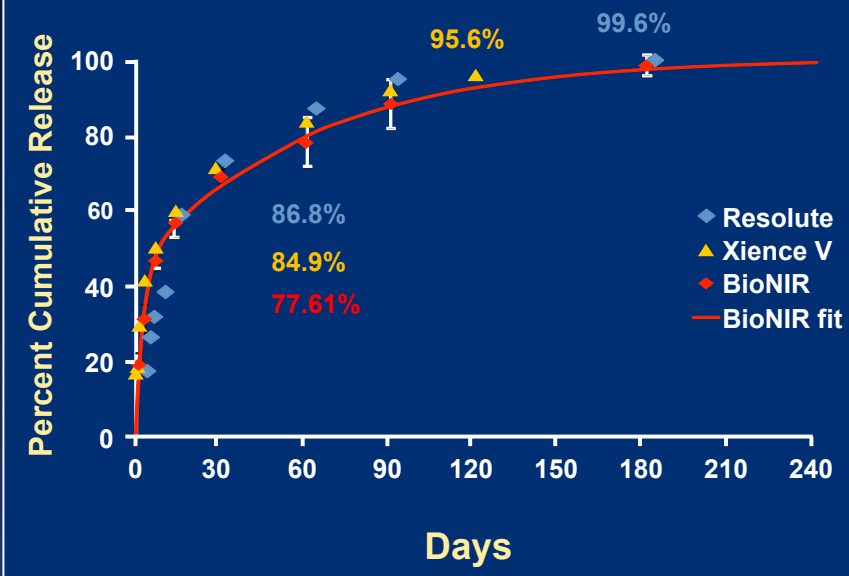
tct2016

Medinol Ltd., Tel Aviv, Israel

Cardiovascular Research Foundation

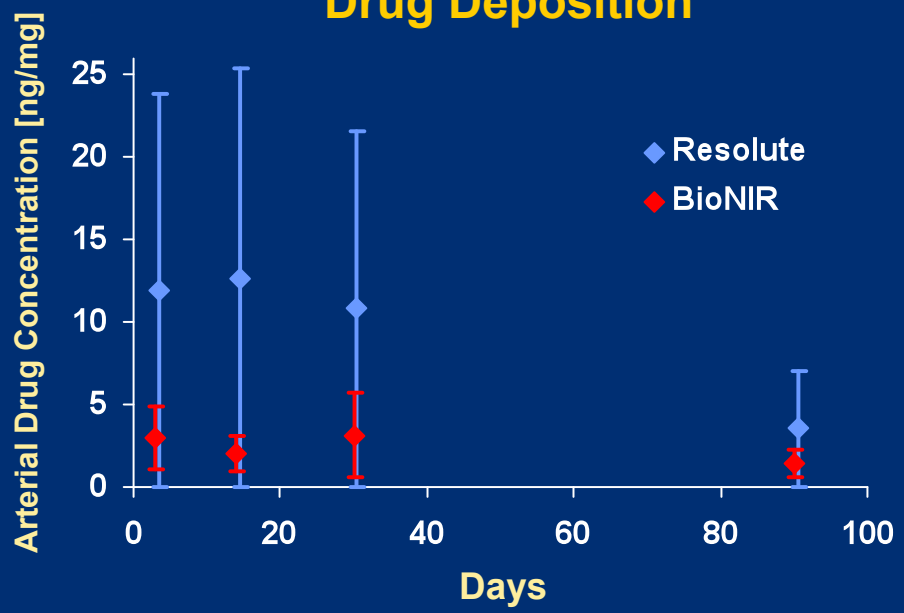
BioNIR Pharmacokinetics

Drug Release



Carter et al TCT 2006
Perkins et al *J Interven Cardiol* 2009;22:S28-S40

Drug Deposition



Yazdani et al *J Invasive Cardiol* 2013

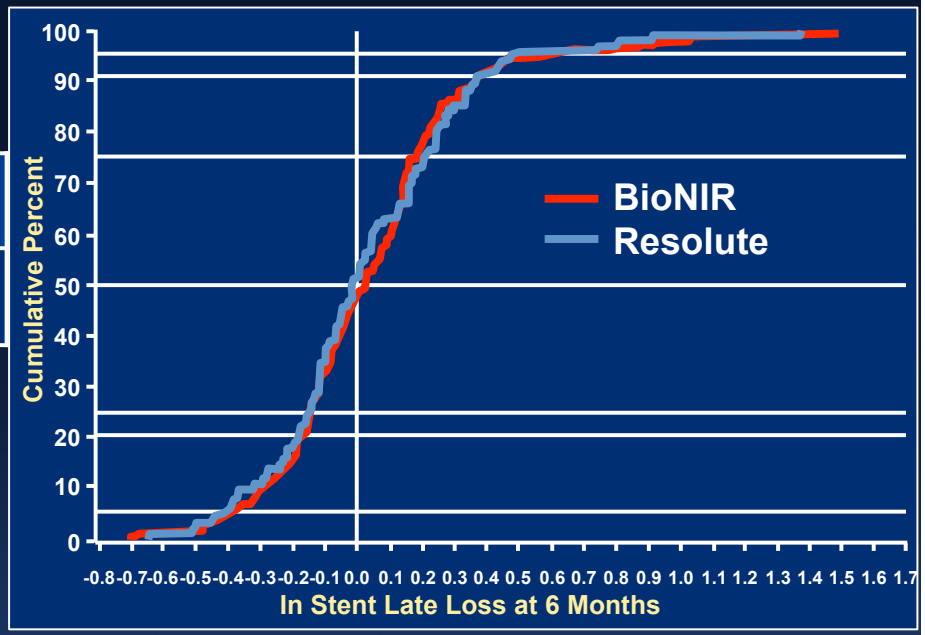
NIREUS

Primary Endpoint 6-month angiographic late loss, N=302

6 Month In-Stent Late Loss

BioNIR	Resolute	$P_{Noninferiority}$
0.042 (0.306)	0.030 (0.308)	<0.0001

Data represented as mm, STD



6 Month Clinical Outcomes

	BioNIR	Resolute	*P* value
TLF	1.5% (3/201)	3.0% (3/101)	0.39
CV Death	0.5% (1/201)	0.0% (0/101)	1.00
Target Vessel MI	1.0% (2/201)	3.0% (3/101)	0.23
Target Lesion Revascularization	1.6% (3/201)	1.0% (1/101)	0.68

Trial Leadership and Organization

- Trial Chair: Gregg Stone, MD
- Principal Investigator: David Kandzari, MD
- Co-PIs: Pieter Smits, MD, PhD & Michael Love, MD
- ARO – Cardiovascular Research Foundation
  - Medical Monitoring – Ori Ben-Yehuda, MD
  - Angiographic Core Lab – Philippe Genereux, MD
  - Safety (CEC/DSMB) – Ioanna Kosmidou, MD, PhD
    - CEC Chair: Stephen Marks, MD – Columbia University
    - DSMB Chair: John Ambrose, MD – UCSF
  - Data Management – Cecilia Hart
  - Statistics – Melek Ozgu Ozan, MSc
- CRO: Novella Clinical
- Sponsor: Medinol Ltd

BIONICS – Trial Design

"More Comers" Population with Symptomatic CAD (eg, NSTEMI, CTO, SVG, MVD)

BioNIR Stent N=958

76 Centers in NA, Europe, Israel
FAS*:1919 patients randomized 1:1

Noninferiority Design
(Event rate 5.8%, Delta 3.3%, Power 90%)

Resolute Stent N=961

Primary Clinical Endpoint

QCA & Imaging Endpoints

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

Key Inclusion Criteria

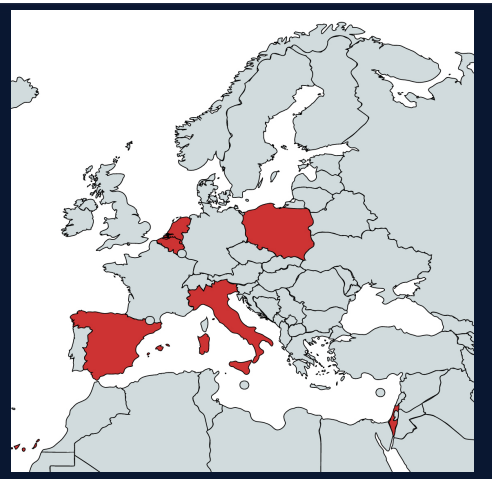
1. Patient with an indication for PCI
    a. NSTEMI
    b. Recent STEMI (>24 hrs)
    c. Angina (Stable and Unstable)
    d. Target lesion diameter stenosis of ≥70%
    c. Positive non-invasive stress test
    d. FFR ≤0.80
2. Target lesion(s) in a native coronary artery or bypass graft conduit with visually estimated diameter of ≥2.5 mm to ≤4.25 mm
3. Complex lesions are allowed including calcified lesions, non-occlusive thrombus, CTO, bifurcation lesions (except planned dual stent implantation), ostial RCA lesions, tortuous lesions, bare metal stent restenotic lesions, protected left main lesions, saphenous vein graft lesions
4. Overlapping stents are allowed

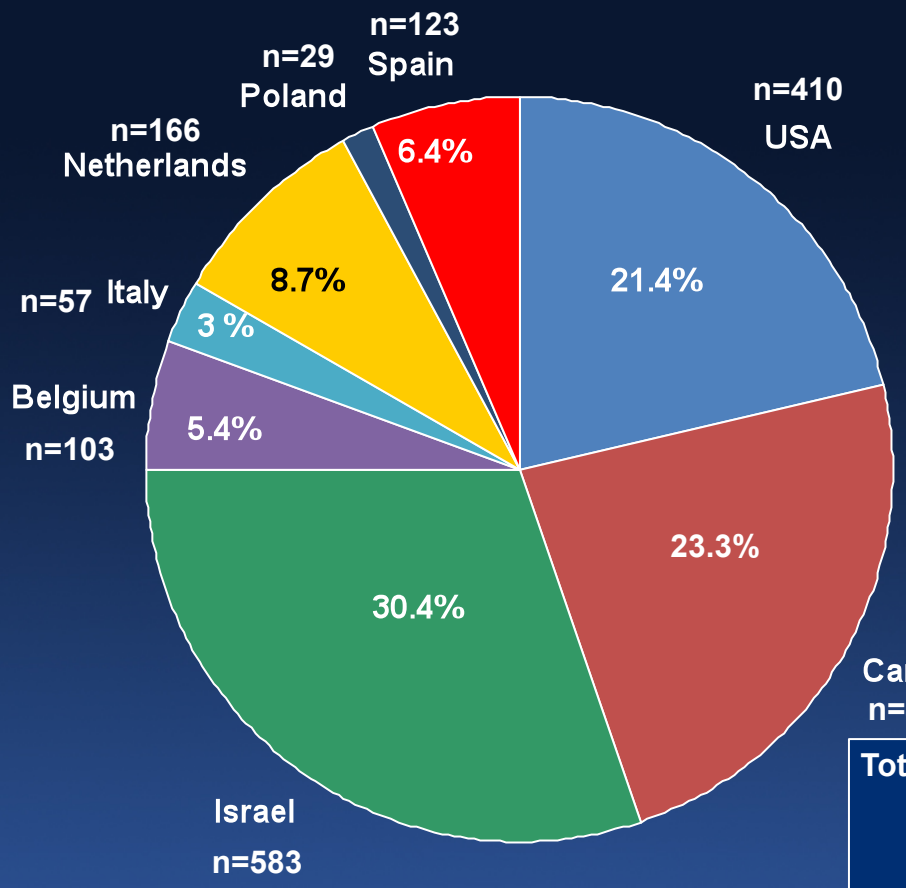
Key Exclusion Criteria

1. History of stent thrombosis
2. Cardiogenic shock
3. Known LVEF <30%
4. Relative or absolute contraindication to DAPT for 12 months (including planned surgeries that cannot be delayed)
5. Subject on or indicated for anticoagulation
6. Severe renal insufficiency (clearance <30 ml/min)

BIONICS Enrollment

76 Enrolling Sites, 8 Countries





Total number randomized and in Full Analysis Set: 1919

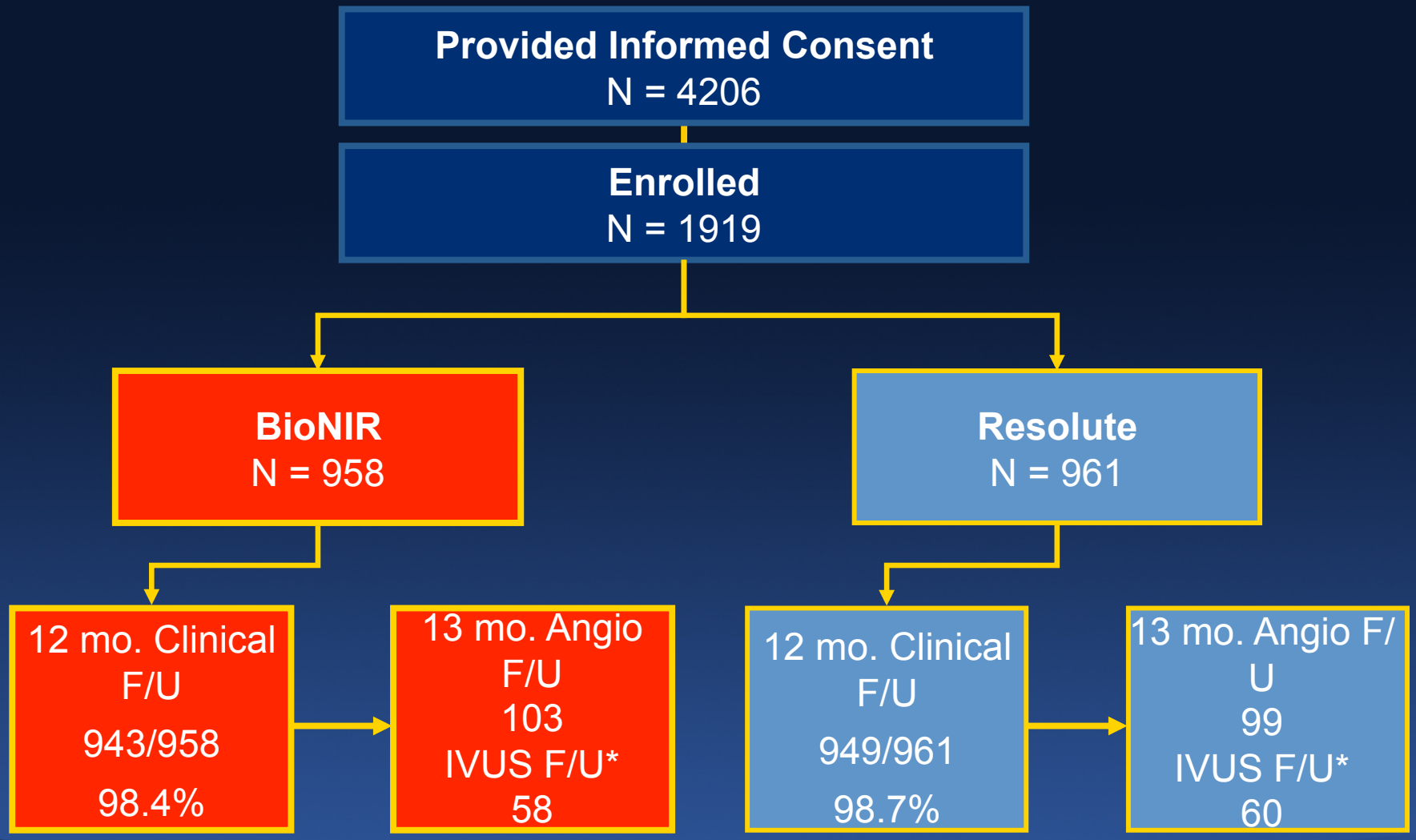
Dates of enrollment:
First: March 13, 2014
Last: August 28, 2015

Cardiovascular Research Foundation

Leading Enrolling Sites

Institution	Number enrolled
Tel-Aviv Souraski Medical Center - Israel	150
Victoria Heart Institute Foundation - Canada	140
Kaplan Medical Center - Israel	126
Rabin Medical Center - Israel	111
Centre Hospitalier Universitaire de Quebec - Canada	109
Hospital Meixoeiro - Spain	88
Hadassah Medical Organisation - Israel	82
Centre Hospitalier de l'Universite de Montreal - Canada	59
Maasstad Ziekenhuis - Netherlands	58
Sha'are Zedek Medical Center - Israel	53
Queen Elizabeth II Health Sciences Centre - Canada	48
CHU de LiÃ¨ge - Belgium	40
Bnai Zion Medical Center - Israel	38
Medical Center Alkmaar - Netherlands	38
Catherina Ziekenhuis - Netherlands	35
MediQuest Research Group - USA	34
North Shore Hospital - USA	34
ZNA Middleheim - Belgium	34
Victoria Heart and Vascular Center - USA	30
Scarborough Cardiology Research - Canada	30
Imeldaziekenhuis - Belgium	29
San Raffaele - Italy	28
Columbia University Medical Center - USA	25

BIONICS
Patient Disposition



* Ongoing

Baseline Clinical Characteristics

	BioNIR (N= 958)	Resolute (N= 961)	*P* value
Age	63.7 ± 10.2	63.2 ± 10.3	0.43
Male	78.3%	81.9%	0.05
Diabetes	32.8%	32.3%	0.81
ACS	40.7%	38.7%	0.37
NSTEMI	35.2%	36.6%	0.56
Current Smokers	23.4%	19.4%	0.03
Hyperlipidemia	80.4%	78.1%	0.21
Hypertension	72.4%	74.0%	0.42
Prior MI	31.1%	30.5%	0.77
Prior PCI	38.8%	38.2%	0.77
Prior CABG	8.8%	9.6%	0.54

Angiographic Characteristics

	BioNIR (N= 958 patients, 1275 lesions)	Resolute (N= 961 patients, 1277 lesions)	*P* value
Target Vessel			
LAD	40.7%	39.8%	0.63
RCA	31.9%	32.2%	0.89
Circumflex	24.4%	25.0%	0.73
Left Main	1.1%	0.4%	0.04
Calcification			
Severe	13.3%	10.5%	0.03
Moderate	13.3%	13.4%	0.92
Tortuosity			
Moderate	4.1%	4.5%	0.63
Severe	3.9%	2.8%	0.10
Bifurcation	28.6%	29.1%	0.78
Ostial Lesion	6.0%	6.1%	0.94

Angiographic Characteristics

	BioNIR N=958 patients, 1275 lesions	**Resolute** N=961 patients, 1277 lesions	***P* value**
Lesion Length	17.6 ± 10.8	17.9 ± 10.7	0.44
No. Target Lesions/pt	1.3 ± 0.6	1.3 ± 0.6	0.51
RVD - pre	2.73 ± 0.49	2.74 ± 0.49	0.69
RVD - post	2.74 ± 0.48	2.76 ± 0.50	0.12
%DS - pre	71.5 ± 13.4	70.7 ± 12.8	0.15
%DS - post	16.4 ± 9.2	16.3 ± 9.9	0.39
Acute Gain (mm)	1.50 ± 0.51	1.50 ± 0.49	0.94
ACC Lesion Class B2/C	57.5%	59.0%	0.45
Stent Length/Lesion	24.3 ± 13.6	24.0 ± 12.5	0.67
Overlapping Stents	24.6%	23.1%	0.43

Procedural Outcomes

	BioNIR N=958 patients, 1275 lesions	**Resolute** N=961 patients, 1277 lesions	***p* value**
Device Success	98.3%	99.5%	0.004
Lesion Success	99.9%	99.8%	1.00
Procedure Success	97.7%	97.3%	0.57

Device success: final in-stent residual QCA diameter stenosis of <50% using the assigned device only and without a device malfunction

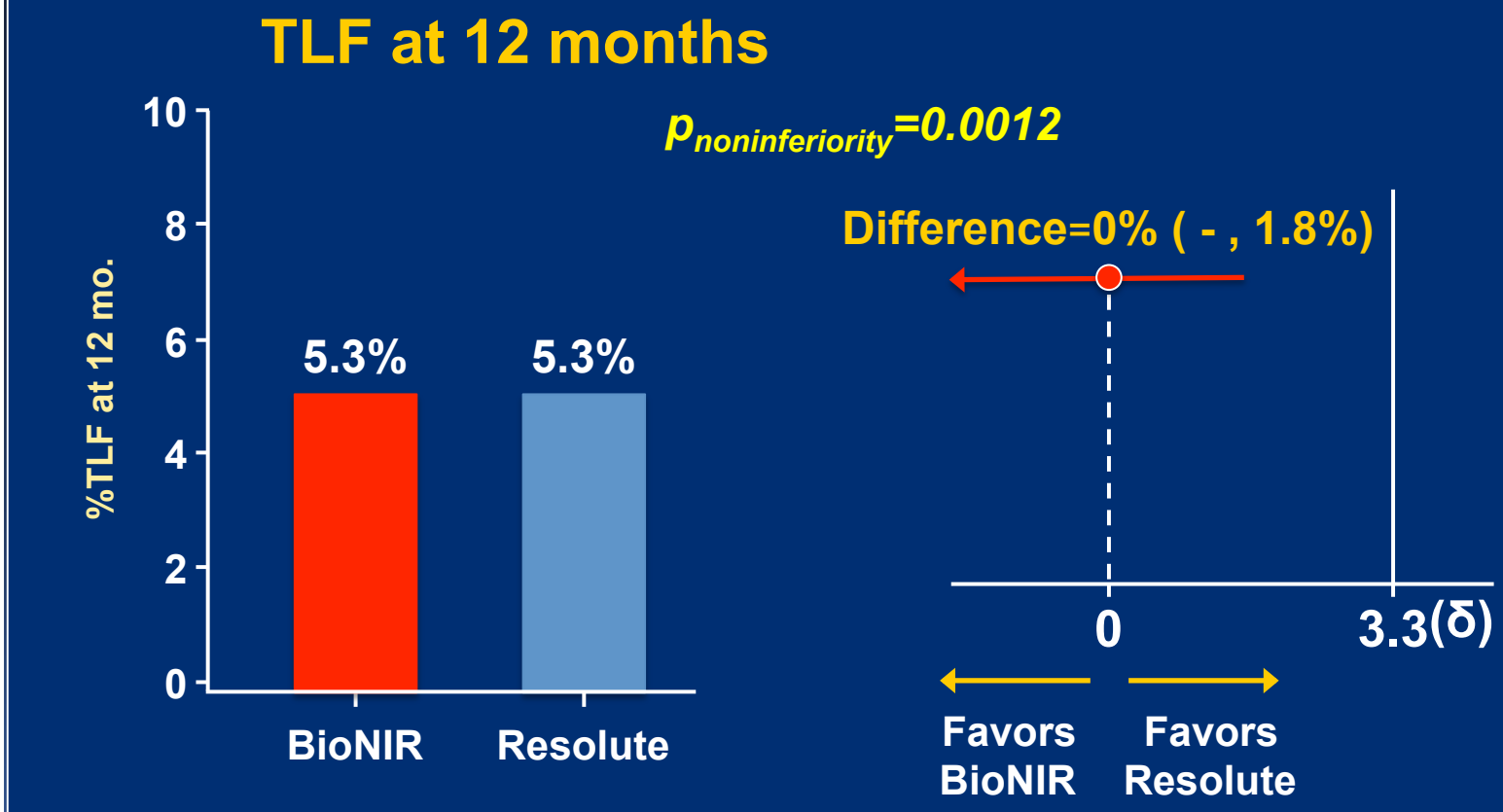
Lesion success: final in-stent residual QCA diameter stenosis of <50% using any percutaneous method

Procedure success: final in-stent QCA diameter stenosis of <50% using the assigned device and/or with any adjunctive devices, without the occurrence of cardiac death, Q wave or non-Q wave MI, or repeat revascularization of the target lesion during the hospital stay

BIONICS
30-day Clinical Outcomes

	BioNIR (N=958)	Resolute (N=961)	Hazard Ratio 95% CI of HR	*P* value
TLF	2.5% (24)	3.2% (31)	0.78 [0.46,1.32]	0.35
Cardiac Death	0.3% (3)	0.1% (1)	3.01 [0.31,28.97]	0.34
TV-MI	2.3% (22)	2.9% (28)	0.79 [0.45,1.38]	0.40
ID-TLR	0.5% (5)	0.5% (5)	1.00 [0.29, 3.47]	1.00

BIONICS – Primary Endpoint

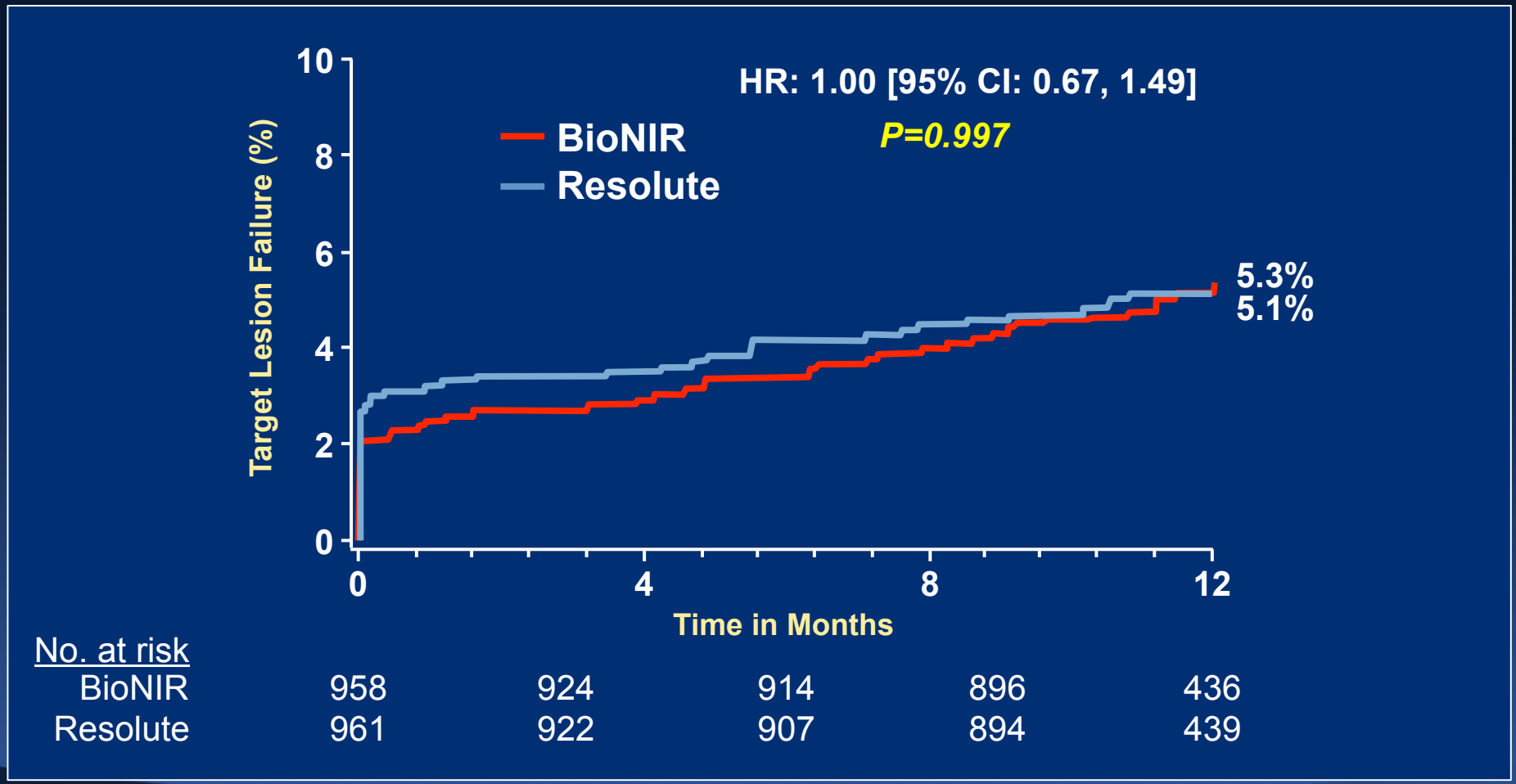


BIONICS
12 mo Key Endpoint Results

	BioNIR N=958	Resolute N=961	Relative Risk	*P* value
Target Lesion Failure (TLF)	5.3% (49/926)	5.3%(49/930)	1.00 [0.68,1.48]	0.98
Cardiac Death	0.5% (5/926)	0.2% (2/930)	2.51 [0.49, 12.91]	0.29
TV-MI*	3.1% (29/926)	3.3% (31/930)	0.94 [0.57, 1.55]	0.81
ID-TLR	3.0% (28/926)	2.4% (22/930)	1.28 [0.74, 2.22]	0.38
Total Mortality	1.2% (11/931)	1.1% (10/936)	1.11[0.47,2.59]	0.82

* SCAI definition for periprocedural MI, Moussa et al. *JACC* 2013

BIONICS
TLF to 12 Months: KM Curves



No. at risk

BioNIR	958	924	914	896	436
Resolute	961	922	907	894	439

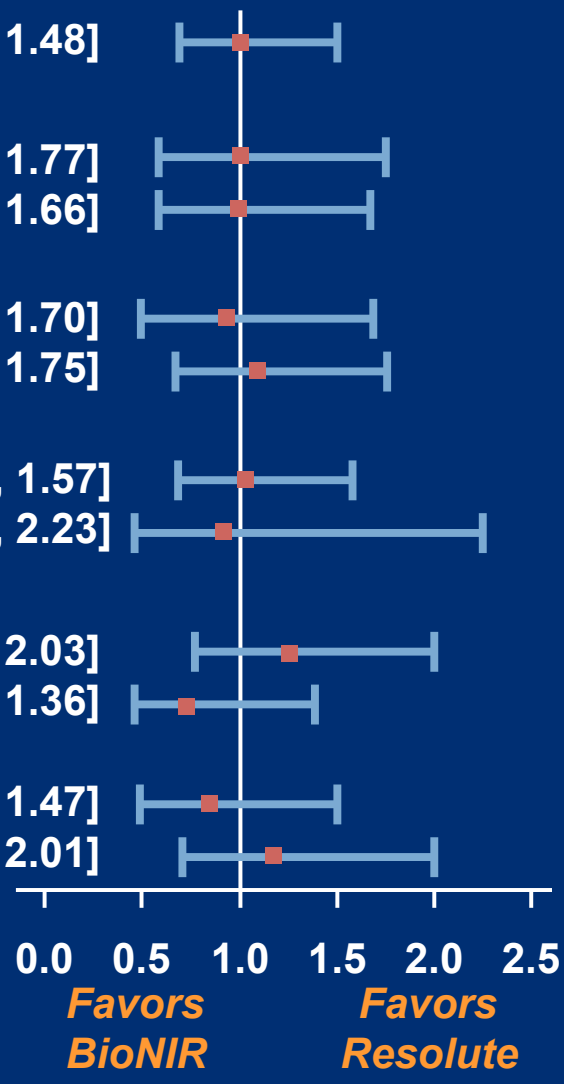
BIONICS
Stent Thrombosis

	BioNIR (N=958)	Resolute (N=961)	*P* value
Stent Thrombosis			
Definite/Probable	0.4% (4/921)	0.6% (6/927)	0.75
Definite	0.4% (4/921)	0.5% (5/926)	1.00
Any Stent Thrombosis	0.4% (4/921)	0.8% (7/928)	0.37
Timing of Event			
Acute ST	0.1% (1/920)	0.1% (1/926)	1.00
Sub-Acute ST	0.3% (3/921)	0.3% (3/927)	1.00
Late	0.0% (0/920)	0.3% (3/927)	0.25

12 Month DAPT Adherence: 75.1% BioNiR, 75.9% Resolute

Target Lesion Failure at 1 Year by Subgroups

Subgroups	12-Month TLF Rate n/ N (%) BioNIR	12-Month TLF Rate n/ N (%) Resolute	Relative Risk [95% CI]	*P* value
Overall	49/926 (5.3%)	49/930 (5.3%)	1.00 [0.68, 1.48]	
Medically Treated Diabetes				0.5
Yes	22/277 (7.9%)	21/264 (7.9%)	1.00 [0.56, 1.77]	
No	27/649 (4.2%)	28/666 (4.2%)	0.99 [0.59, 1.66]	
Acute Coronary Syndrome (ACS)				0.39
ACS	18/380 (4.7%)	19/363 (5.2%)	0.91 [0.48, 1.70]	
No ACS	31/546 (5.7%)	30/567 (5.3%)	1.07 [0.66, 1.75]	
Sex				0.46
Male	39/725 (5.4%)	40/762 (5.3%)	1.03 [0.67, 1.57]	
Female	10/201 (5.0%)	9/168 (5.4%)	0.93 [0.39, 2.23]	
Age				0.19
>=65 Year	33/433 (7.6%)	27/441 (6.1%)	1.24 [0.76, 2.03]	
<65 Year	16/493 (3.3%)	22/489 (4.2%)	0.72 [0.38, 1.36]	
Region				0.28
North America	22/420 (5.2%)	25/402 (6.2%)	0.84 [0.48, 1.47]	
Outside of N. Am.	27/506 (5.3%)	24/528 (4.6%)	1.17 [0.69, 2.01]	



Interaction p value: Gail-Simon test for qualitative interactions (interaction between the treatment and the subgroup variable)

BIONICS
Conclusions

- In the present large-scale, ‘more comers’ trial, the BioNIR ridafirolimus-eluting stent was non-inferior to the Resolute stent for the primary endpoint of target lesion failure at 1 year, and resulted in low rates of target lesion revascularization and stent thrombosis
- These findings endorse the safety and efficacy of BioNIR in patients representative of real world clinical practice