ENDEAVOR II

A Randomized Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver™ Coronary Stent in De Novo Native Coronary Artery Lesion

W. Wijns, J. Fajadet, and R. Kuntz,
for the ENDEAVOR II investigators

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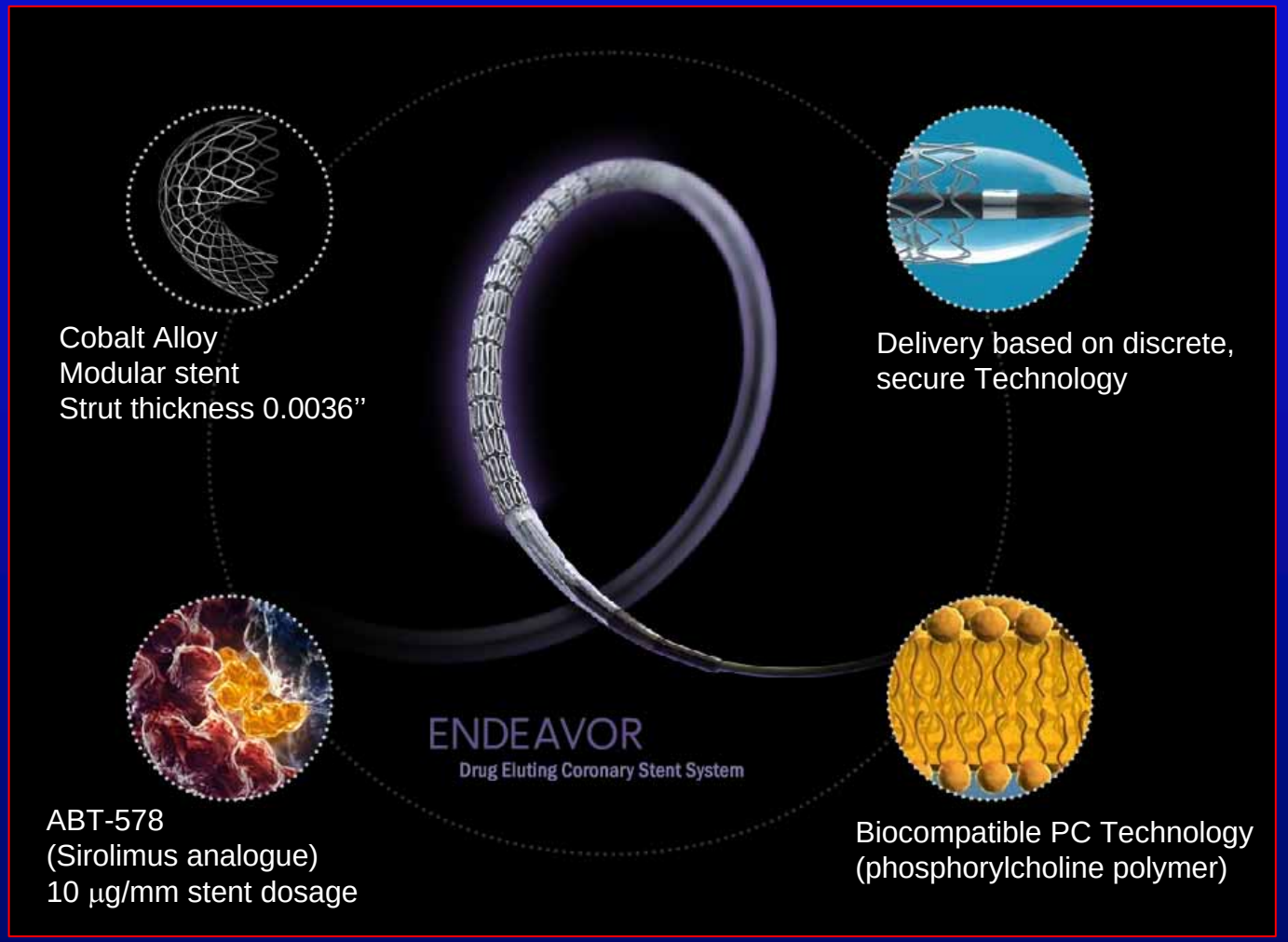
Components of the Endeavor Stent



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ABT-578

- **NCE**
  - Discovered by Abbott Laboratories in 1996
  - First NCE to reach large scale clinical trials
  - Tetrazole containing macrocyclic immunosupressant
  - Molecular Formula: C52 H79 N5 012
  - Lipophilic with low water solubility
  - Anti-proliferative and anti-inflammatory agent; binding to FKBP-12; Inhibition of mTOR activity
  - Stable in solid state at room temperature
  - Drug dose contained on the coated stent is 10 μg/mm
  - Extensively evaluated in preclinical and early clinical studies

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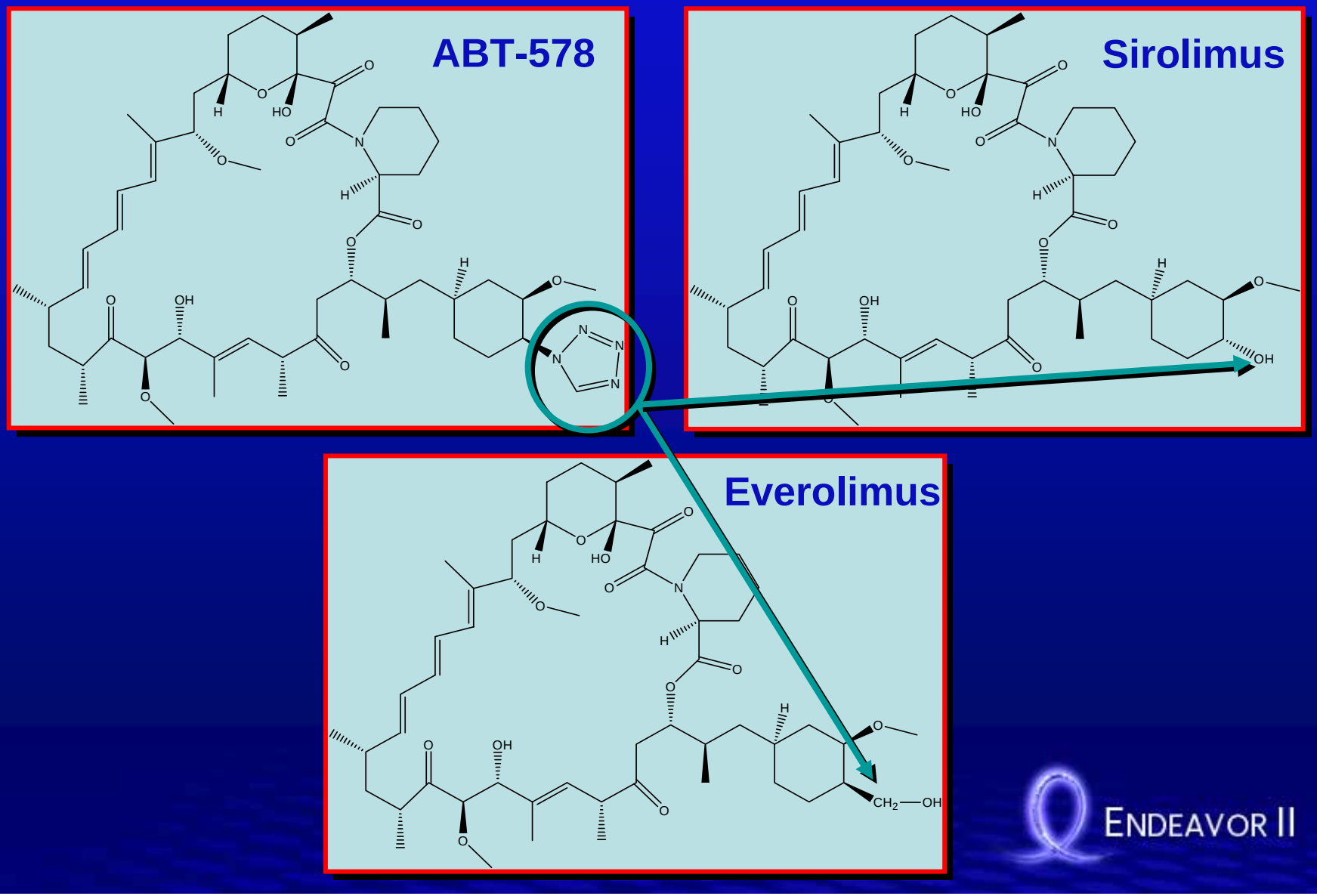
ABT-578 Chemical Structure



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Randomized, Double-Blind Trial

Single De Novo Native Coronary Artery Lesions
Stent Diameters: 2.25-3.5 mm
Stent Lengths: 18-30 mm (8/9 mm bailout)
Lesion Length: 14-27 mm
Pre-dilatation required

Driver Stent
(Control arm)
n=600

1200 pts, 72 sites
Global OUS Study

Endeavor Stent
(Active arm)
n=600

Clinical/MACE

30d | 6mo | 8mo | 9mo | 12mo | 2yr | 3yr | 4yr | 5yr

Angio/IVUS

Angio n=first 600
IVUS n=first 300
IVUS for overlapping stents

- Primary Endpoint: TVF (cardiac death, MI, TVR) at 9 months
- PK assessment sub-study (N=106)
- Dual antiplatelet therapy for 3 months
- 10 μg ABT-578 per mm stent length on PC biomimetic coating

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Power Calculations for Primary Endpoint

- We assumed a reduction in 9-month target vessel failure rate from 16.0% to 9.5% (40% treatment effect)
- The power of the study was 90%
- The two-sided alpha error was 5%
- The calculated sample size was 552 subjects per arm, or 1104 required evaluable subjects
- A total of 1200 patients were enrolled to account for errors in the assumptions and for subjects lost to follow-up

Core Laboratories

QCA Core Lab

- Brigham and Women's Hospital, Boston, MA, USA
  Jeffrey J. Popma, MD

IVUS Core Lab

- Cardiovascular Core Analysis Lab
  Stanford Interventional Cardiology, CA, USA
  Peter Fitzgerald, MD

ECG Core Lab

- Harvard Clinical Research Institute, Boston, MA, USA
  Peter Zimetbaum, MD

Data Coordinating Center

- Harvard Clinical Research Institute
  Ralph D'Agostino, PhD

Clinical Events Committee/DSMB

- Harvard Clinical Research Institute, Boston, MA, USA
  Donald Cutlip, MD

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Clinical Sites

Investigator	Hospital	Patients
G. Laarman	Onze Lieve Vrouwe Gasthuis, Amsterdam	66
K-H. Kuck	Krankenhaus Sankt Georg, Hamburg	54
J. Ormiston	Mercy Hospital, Auckland	54
T. Münzel	Universitätsklinikum, Hamburg-Eppendorf	47
E. Hauptmann	Krankenhaus der Barmherzigen Brüder, Trier	42
M. Suttorp	St. Antonius Ziekenhuis, Nieuwegein	41
J. Drzewiecki	Katowice University Hospital, Katowice	41
M. Pieper	Herzzentrum Bodensee, Kreuzlingen	37
H-P. Schultheiss	Universitätsklinikum Benjamin Franklin, Berlin	37
W. Ruzyllo	Institute of Cardiology Warsaw, Warsaw	33
P. Pieniazek	John Paul II Hospital, Krakow	33
H. Heuer	Medizinische Klinik St. Johannes, Dortmund	32
E. Grube	Krankenhaus & Herzzentrum, Siegburg	32
B. Hennen	Universitätskliniken des Saarlandes, Homburg	29
J. Bonnier	Catharina Ziekenhuis, Eindhoven	28
R. Kornowski	Beilinson Hospital, Petach Tikva	28
A. Zeiher	Klinikum der J-W Goethe, Frankfurt	27

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Clinical Sites (cont)

Investigator	Hospital	Patients
E. Camenzind	University Hospital, Geneva	25
R. Whitbourn	St. Vincents Hospital, Melbourne	21
C. Hamm	Kerckhoff Klinik, Bad Nauheim	20
W. Chan	National Heart Center, Singapore	20
A. Lekston	Slaskie Centrum Chorob Serca, Zabrze	19
W. Rutsch	Universitatsklinikum Charité, Berlin	18
C. Lotan	Hadassah University Hospital, Jerusalem	18
P. Kay	Dunedin Hospital, Dunedin	17
F. Schiele	CHU Jean Monjoz, Besancon	17
R. Simon	Universitatsklinikum, Kiel	16
W. Wijns	Onze Lieve Vrouw Ziekenhuis, Aalst	16
B. Lewis	Lady Davis Carmel Medical Center, Haifa	16
P. Sick	Universitat Leipzig Herzzentrum, Leipzig	16
D. Glogar	AKH Wein, Vienna	15
R. Beyar	Rambam Medical Center, Haifa	15
J. Motwani	Derriford Hospital, Plymouth	14
D. Muller	St. Vincents Hospital Sydney, Sydney	14

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Clinical Sites (cont)

Investigator	Hospital	Patients
I. Meredith	Monash Medical Center, Clayton, Melbourne Victoria	13
M. Vrolix	ZOL Campus St. Jan, Genk	13
O. Darremont	Clinique Saint-Augustin, Bordeaux	13
W. Jukema	Leiden University Medical Center, Leiden	12
P. Vermeersch	AZ Middelheim, Middelheim	12
L. Thuessen	Skejby Hospital, Arhus	11
R. Hoffmann	Medical Clinic University Aachen, Aachen	11
L. Michalis	University Hospital of Ioannina, Ioannina	11
D. Carrie	Hospital de Rangueil – CHU, Toulouse	10
F. Fajadet	Clinique Pasteur, Toulouse	10
F. Eberli	University of Zürich, Zürich	9
C. De Cock	AZVU, Amsterdam	8
C. Dubois	University Hospital Gasthuisberg, Leuven	8
J. Quininha	Hospital de Santa Marta, Lisbon	8
N. Uren	Royal Infirmary, Edinburgh	8
O. Kwok	Grantham Hospital, Hong Kong	7
C. Tan	National University Hospital, Singapore	7
A. Zaman	Freeman Hospital, Newcastle	7

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Clinical Sites (cont)

Investigator	Hospital	Patients
J. Boland	Hospital de la Citadelle, Liege	6
F.J. Neumann	Herz-Zentrum, Bad Krozingen	6
G. Grollier	Centre Hospitalier Universitaire, Caen	6
O. Pachinger	LKH Innsbruck, Innsbruck	5
P. Richard	Centre Hospitalier Saint Martin, Caen	5
J.M. Juliard	Hospitalier Bichat-Claude Bernard, Paris	5
P. Henry	AP-HP Hoptial Lariboisiere, Paris	5
S. Silber	Private Praxis Muenchen	4
D. Crochet	Hospital Guillaume et Tene Laennel, Nantes	3
P. Coste	Hospital Cardiologique du Haut Leveaue, Pessac	3
H. Kelbaek	Righspitalet The Heart Centre, Copenhagen	2
A. Banning	John Radcliff Hospital, Oxford	2
Y. Louvard	Institute Hospitalier Jacques Cartier, Massy	2
K.D. Dawkins	Southampton General Hospital, Southampton	2
V. Guetta	Sheba Medical Center, Tel Hashomer	2
T. Gershlick	Glenfield Hospital, Leicester	2
V. Legrand	CHU Sart Tilman, Liege	1

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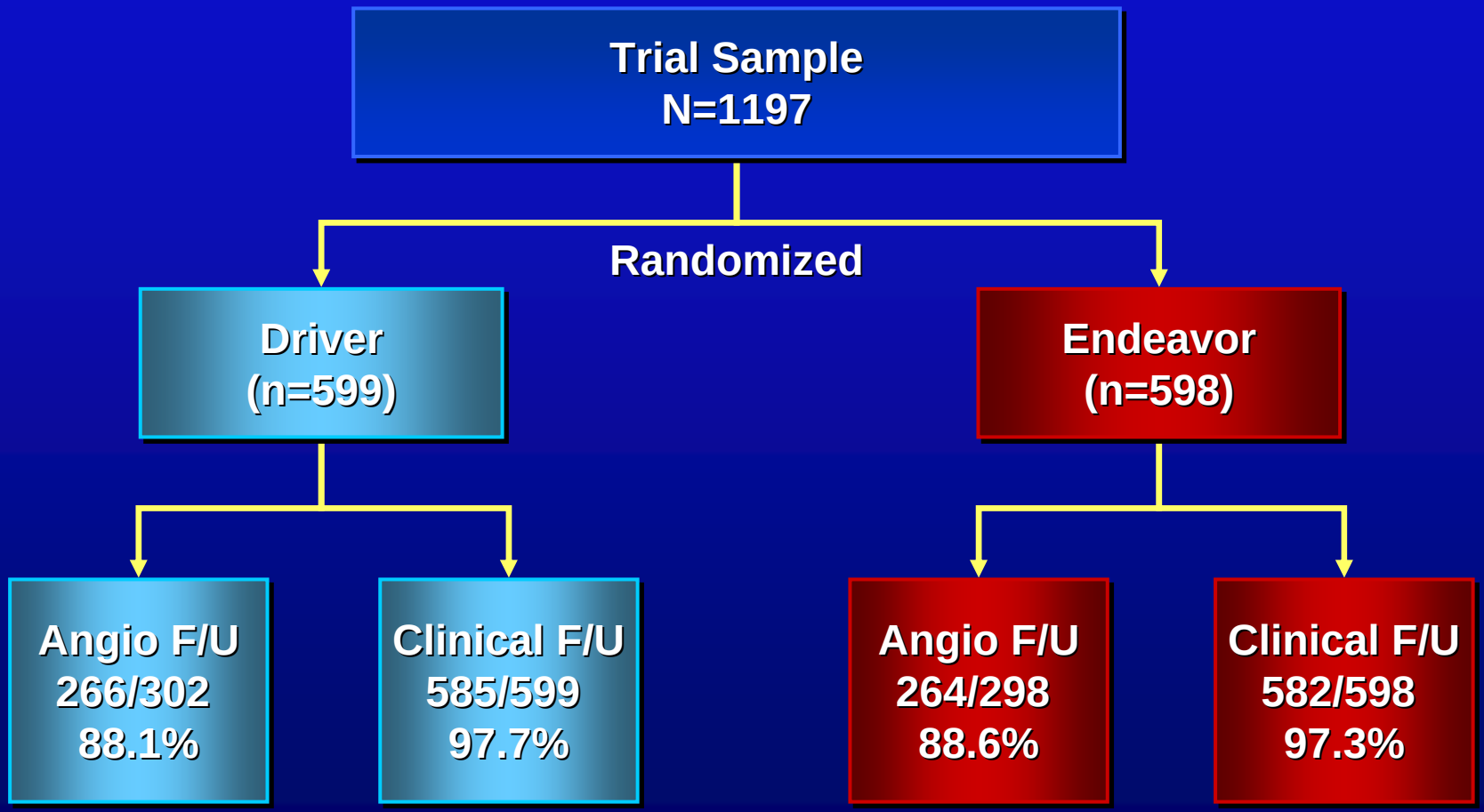
Trial Flow



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Patient Demographics

	Driver n=599	Endeavor n=598	*p* value
Male Gender (%)	75.3	77.2	ns
Age (years)	61.9 ± 10.5	61.6 ± 10.5	ns
Prior MI (%)	41.5	39.7	ns
Prior PCI (%)	18.0	21.7	ns
Diabetes Mellitus (%)	22.2	18.0	ns
Unstable Angina (%)	30.3	30.3	ns
Recent MI (%)	14.5	16.1	ns
Hyperlipidemia (%)	76.9	80.5	ns
Current Smoker (%)	35.2	35.3	ns

Baseline Angiography

	Driver n=599	Endeavor n=598	*p* value
LAD (%)	47.5	43.4	ns
B2/C Lesions (%)	78.9	78.4	ns
RVD (mm)	2.76	2.74	ns
Lesion Length (mm)	14.39	14.05	ns
Pre-Procedure MLD (mm)	0.84	0.83	ns
Post-Index Procedure			ns
In-Stent MLD (mm)	2.61	2.59	ns
In-Stent Acute Gain (mm)	1.77	1.76	ns
In-Stent DS (%)	6.3	6.1	ns
In-Segment MLD (mm)	2.24	2.21	ns
In-Segment DS (%)	20.2	20.6	ns

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Procedure Characteristics

	Driver n=589	Endeavor n=588	*p* value
Stent Diameter (mm)	3.10	3.10	ns
Stent Length (mm)	23.2	23.3	ns
Stent :Lesion Length	1.79	1.84	ns
Stents per Lesion	1.11	1.12	ns
Overlapping Stents, n (%)	48 (8)	52 (9)	ns
Overlapping or Abutting	57 (10)	59 (10)	ns
Balloon:Artery Ratio	1.16	1.17	ns
IIbIIIa Inhibitor Use (%)	10.4	13.2	ns
Max Inflation Pressure (atm)	14.6	14.3	ns

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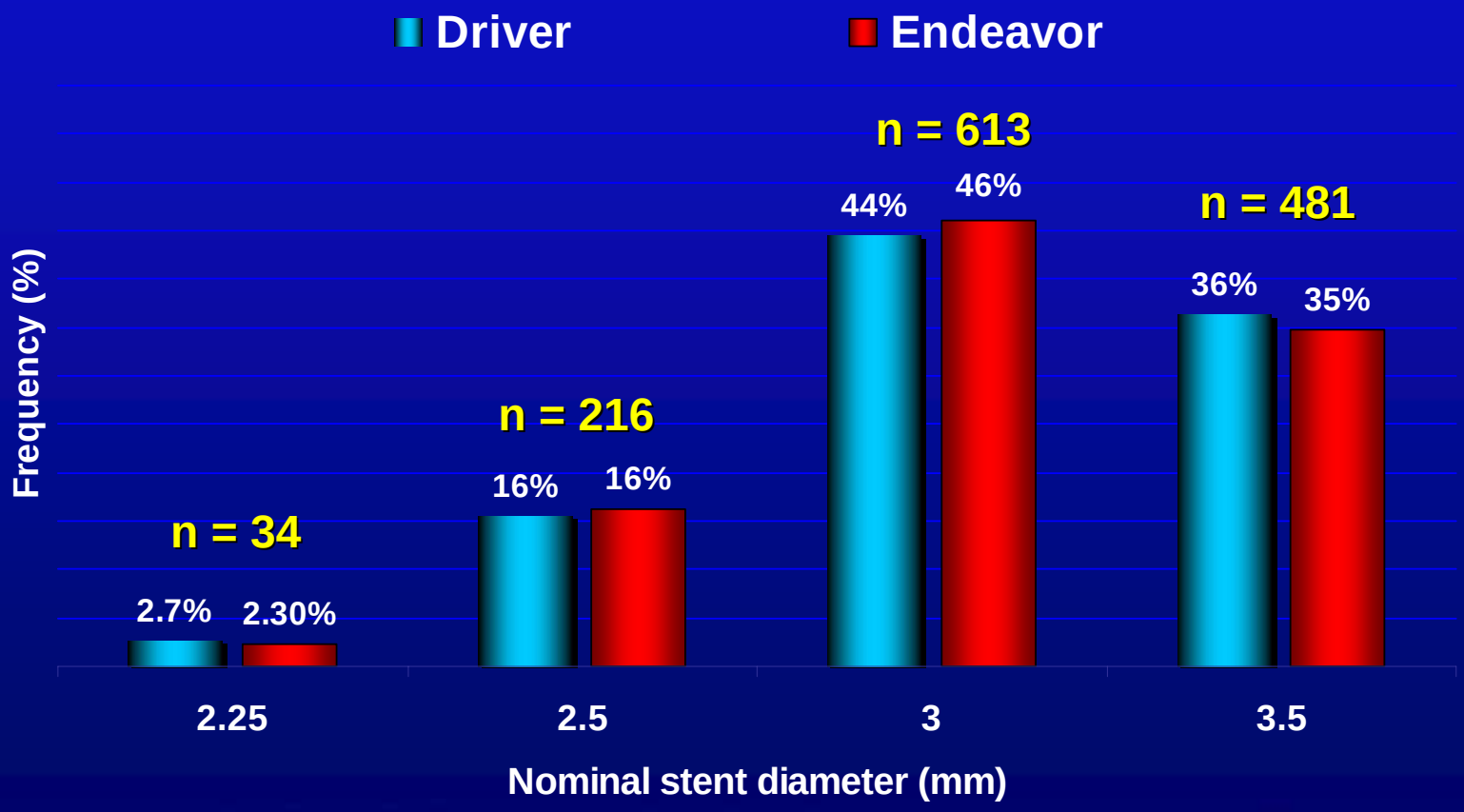
EII Stent Diameter



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Procedure Results

	Driver n=589	Endeavor n=588	*p* value
Lesion Success	100.0%	99.8%	ns
Device Success	99.3%	99.3%	ns
Procedure Success	97.4%	97.1%	ns

Lesion success defined as achievement of <50% residual in-segment percent diameter stenosis

Device success defined as achievement of <50% residual in-segment percent diameter stenosis with assigned stent

Procedure success defined as achievement of <50% residual in-segment percent diameter stenosis with assigned stent and without 30-day MACE

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Clinical Events

In-Hospital

	Driver (N=585)	Endeavor (N=582)	*p* value
Death	0.0% (0)	0.2% (1)	ns
MI (all)	2.7% (16)	2.6% (15)	ns
Q-wave	0.3% (2)	0.2% (1)	ns
Non–Q-wave	2.4% (14)	2.4% (14)	ns
TLR (all)	0.3% (2)	0.5% (3)	ns
TVR (non-TL)	0.0% (0)	0.0% (0)	ns
MACE	2.9% (17)	2.6% (15)	ns
TVF	2.9% (17)	2.6% (15)	ns

Procedural Complications

	Driver n=585	Endeavor n=582
CVA	0.5% (3)	0.2% (1)
Major Bleeding	2.2% (13)	1.2% (7)
Vascular	1.2% (7)	0.5% (3)
Perforation*	0.3% (2)	0.5% (3)

*Both clinical and angiographic included.
p = ns for all comparisons.

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Primary Endpoint

- Target Vessel Failure (TVF) rate at 9 months post procedure
- TVF is a composite of target vessel revascularization, Q- or non Q-wave MI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel

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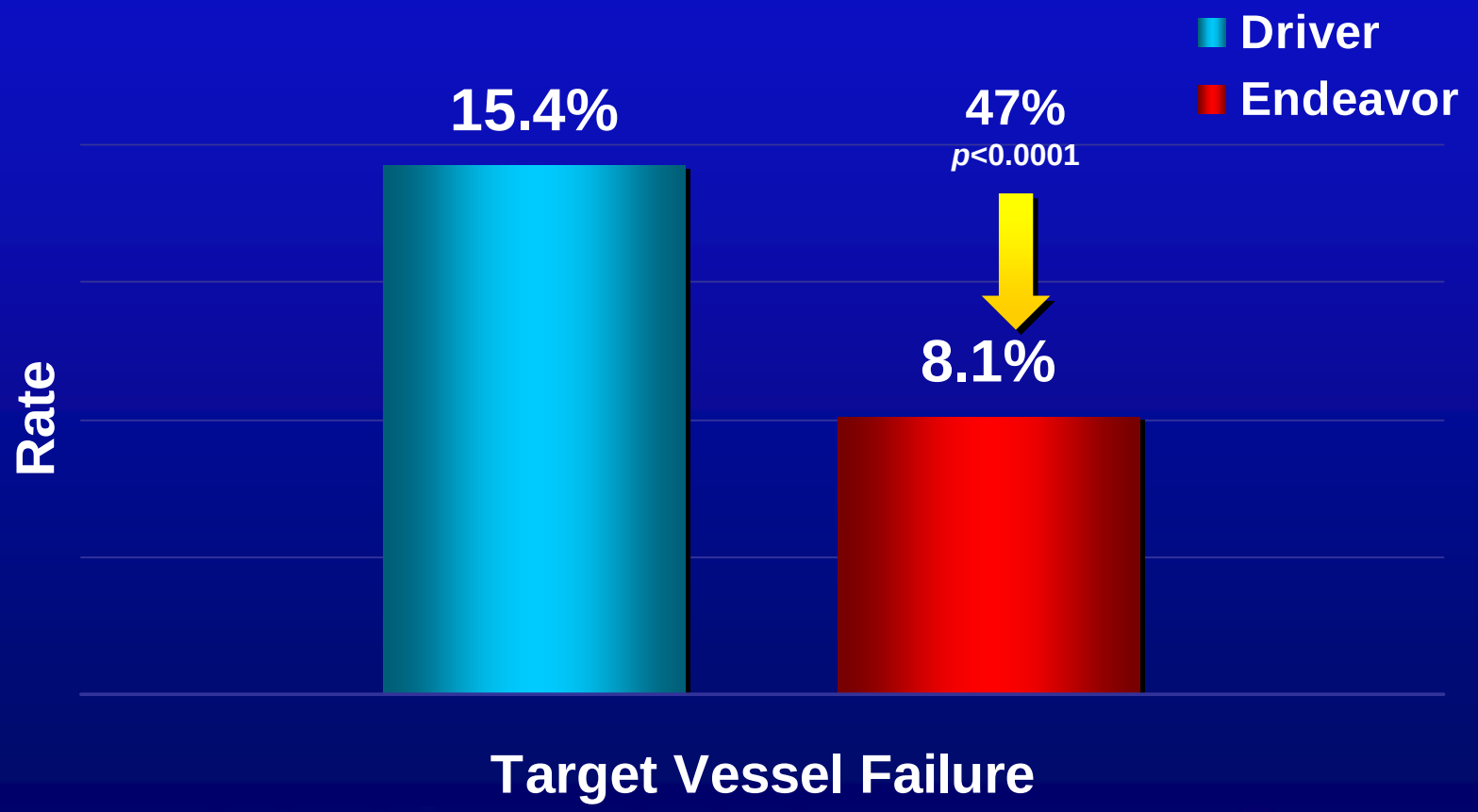
EII Primary Study Endpoint

9 Month Follow-Up



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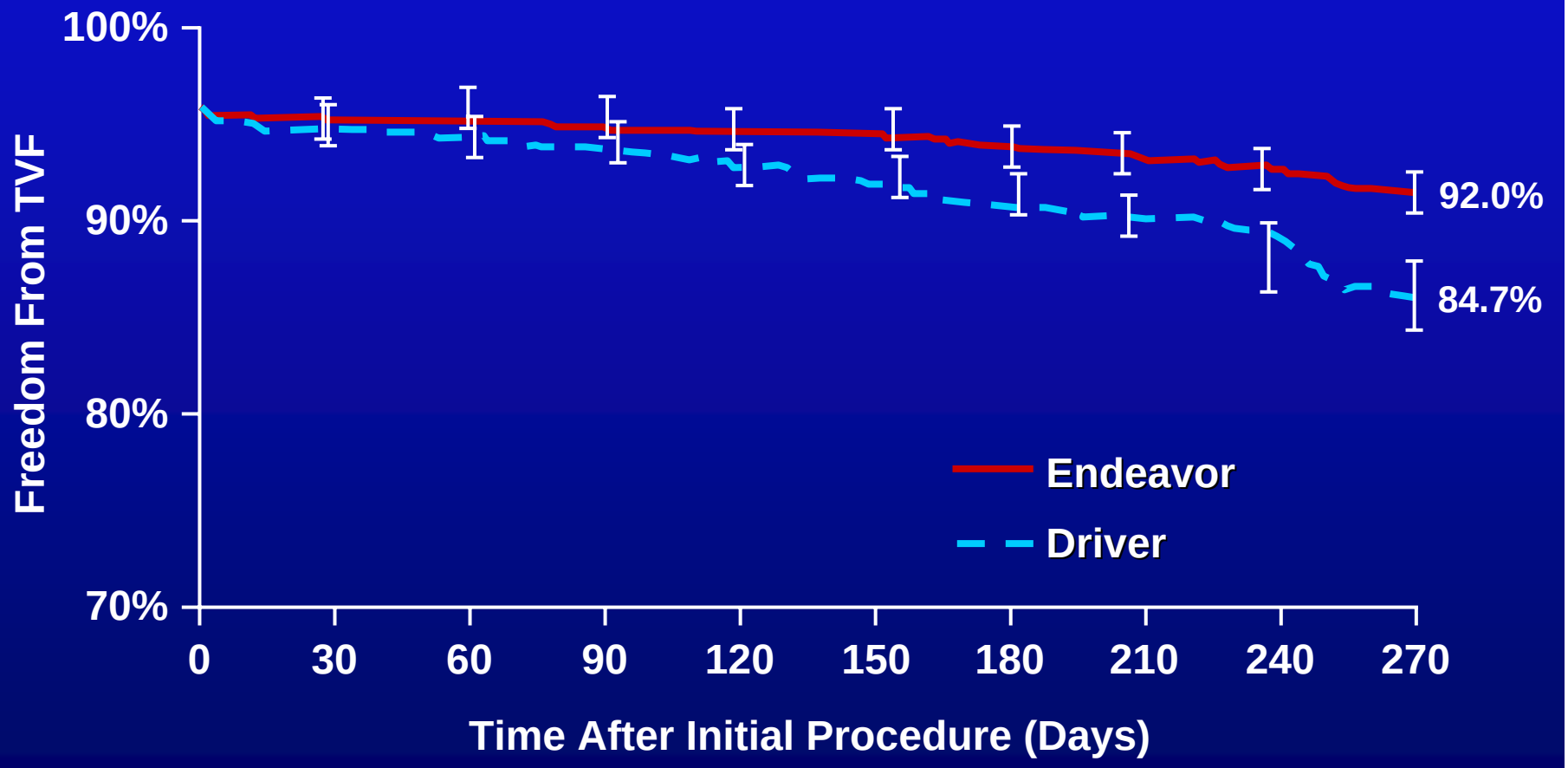
TVF-Free Survival



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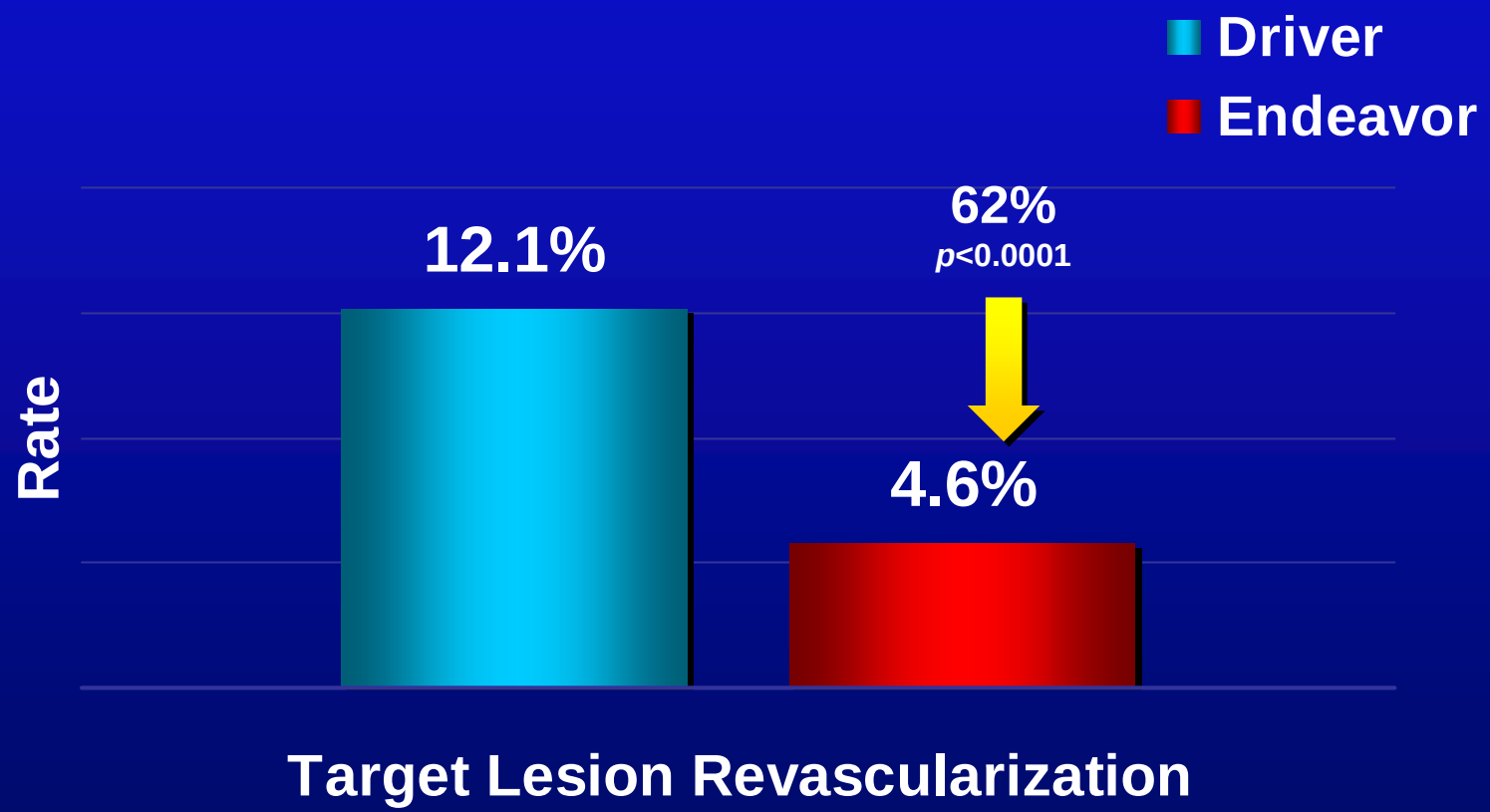
Clinical Restenosis Outcomes

9 Month Follow-Up



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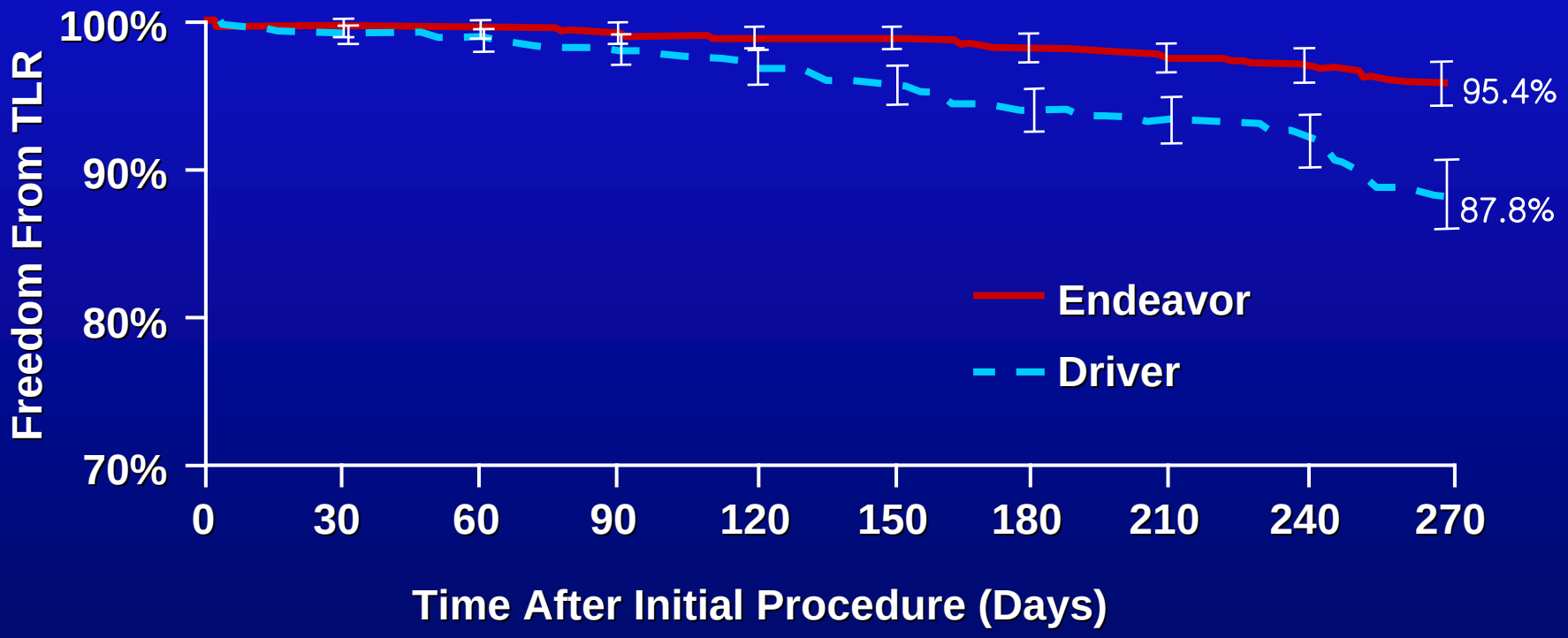
TLR-Free Survival



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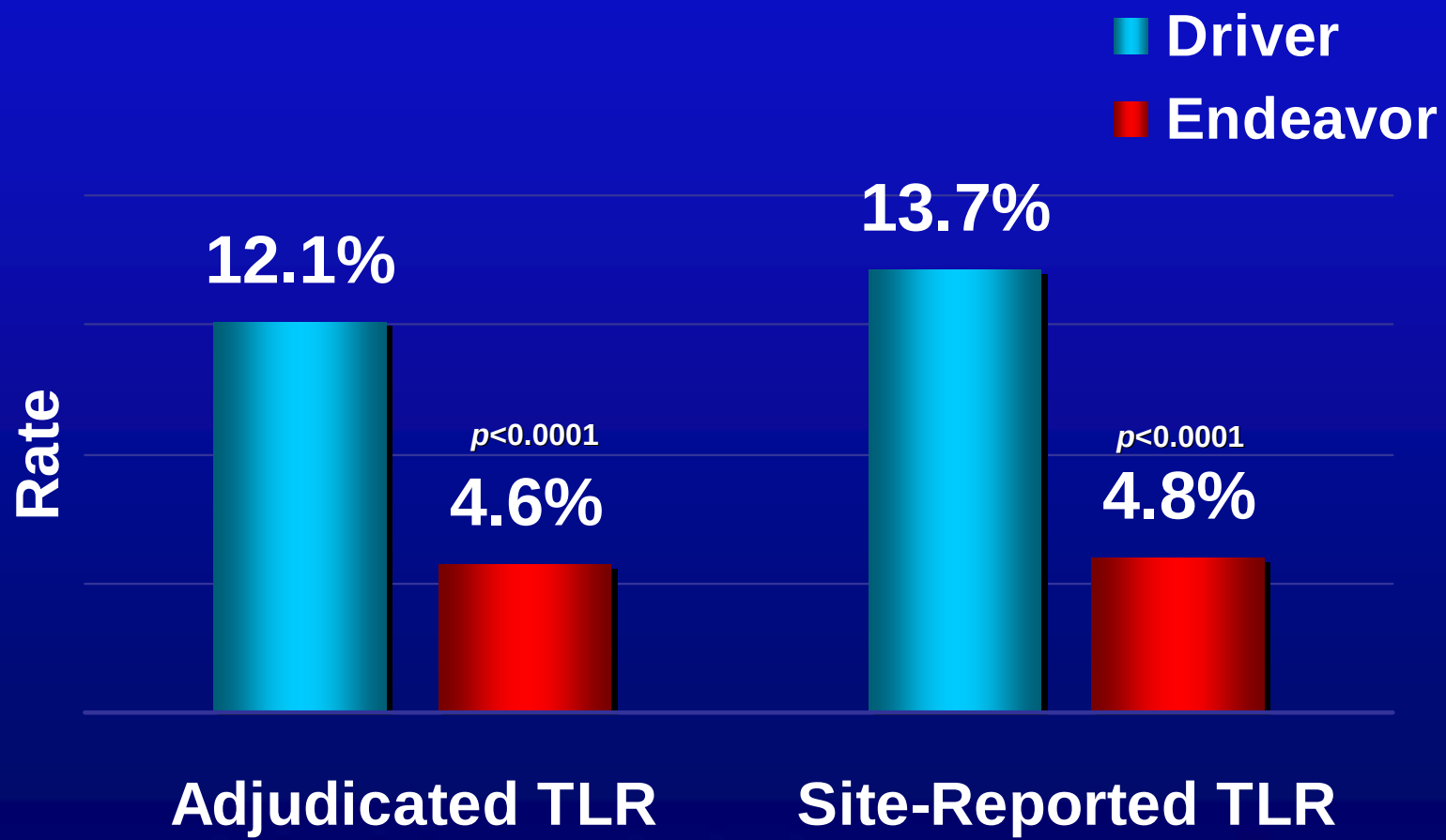
Clinical Restenosis Outcomes

9 Month Follow-Up: Adjudicated vs Site-Reported



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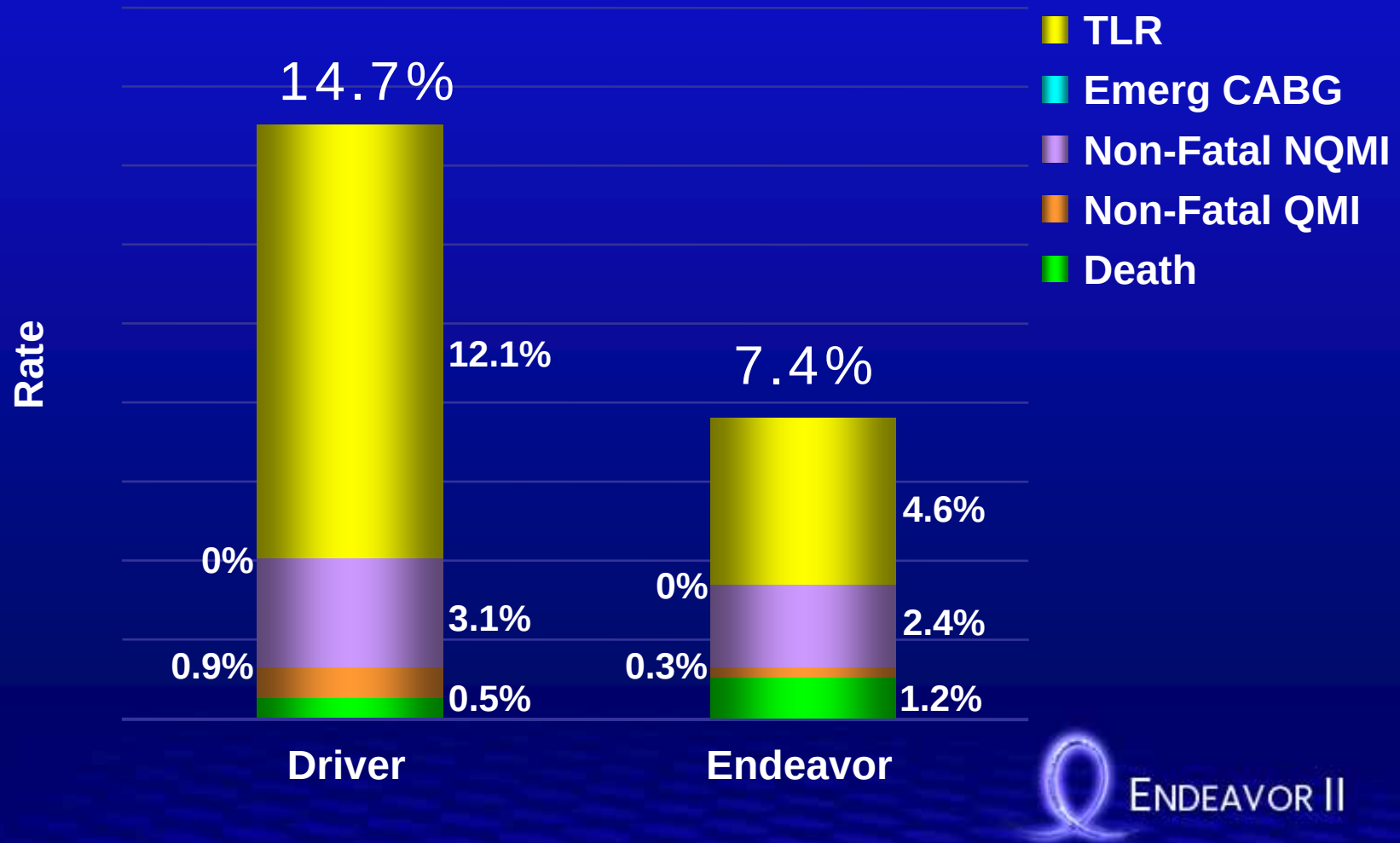
EII MACE

Secondary Endpoint Results to 9 Months



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9 Month Mortality

	Driver n=585	Endeavor n=582	*p* value
Death	**3 (0.5%)**	**7 (1.2%)**	**0.22**
Cardiac†	**3**	**5**	
Non-Cardiac	**0**	**2***	

† Defined as death due to myocardial infarction, cardiac perforation or tamponade, arrhythmia, stroke within 30 days of the procedure or related to the procedure, death due to a complication of the procedure, and any death in which a cardiac cause cannot be excluded, as adjudicated by blinded clinical events committee.

* 2 of 7 deaths non-cardiac (1 lung cancer, 1 cerebral hemorrhage)

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*9 Month Non-Cardiac Mortality**

Treatment	Post-Procedure Day	Cause
Endeavor	39	Metastatic lung cancer
Endeavor	262	Intracerebral hemorrhage

*As adjudicated by blinded clinical events committee.

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Subset Analyses

- Angio vs clinical
- RVD
- Lesion length
- Diabetes (IDDM vs non-IDDM)

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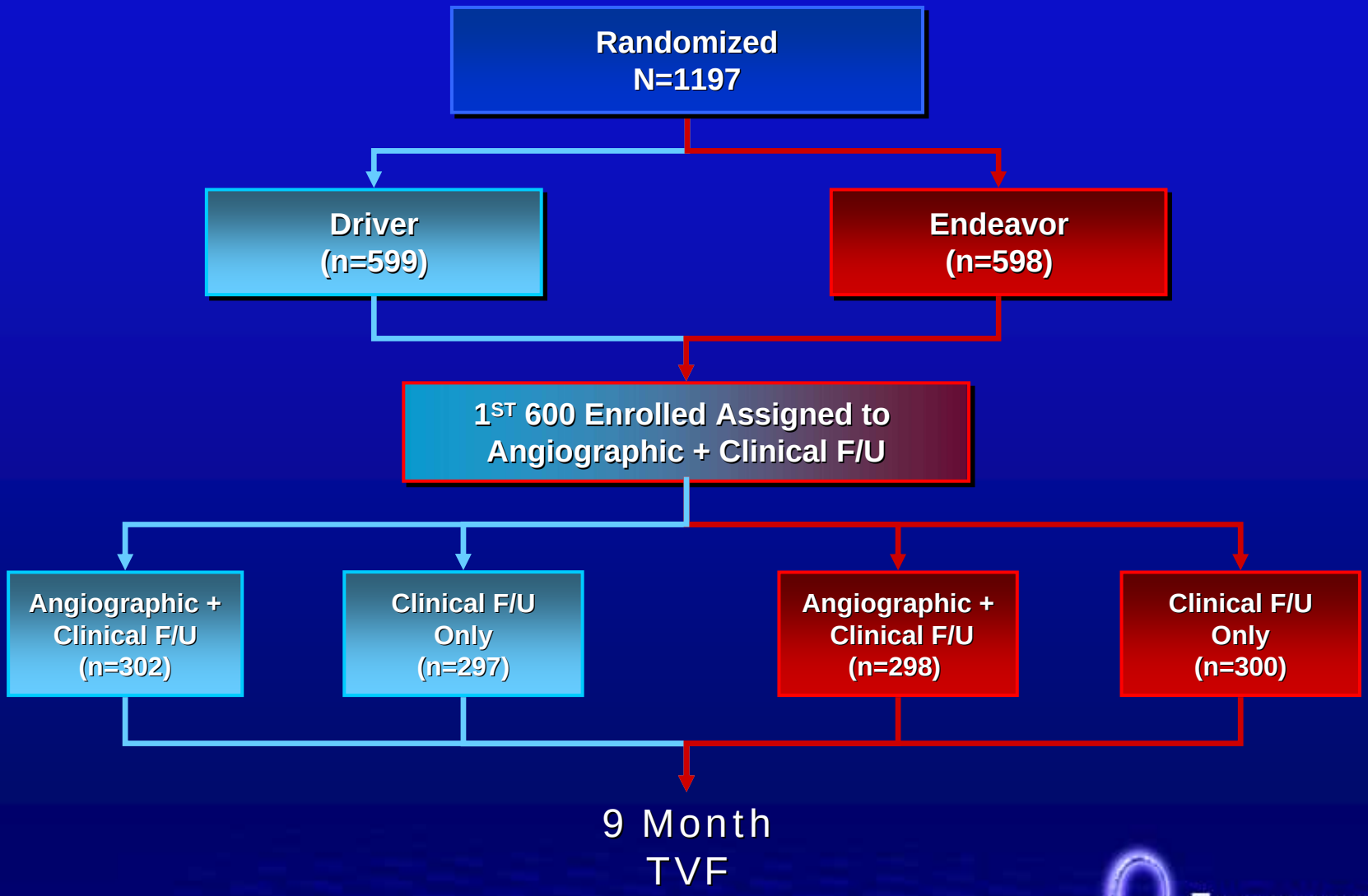
Trial Flow



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Randomized, Double-Blind Trial

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IVUS for overlapping stents

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- PK assessment sub-study (N=106)
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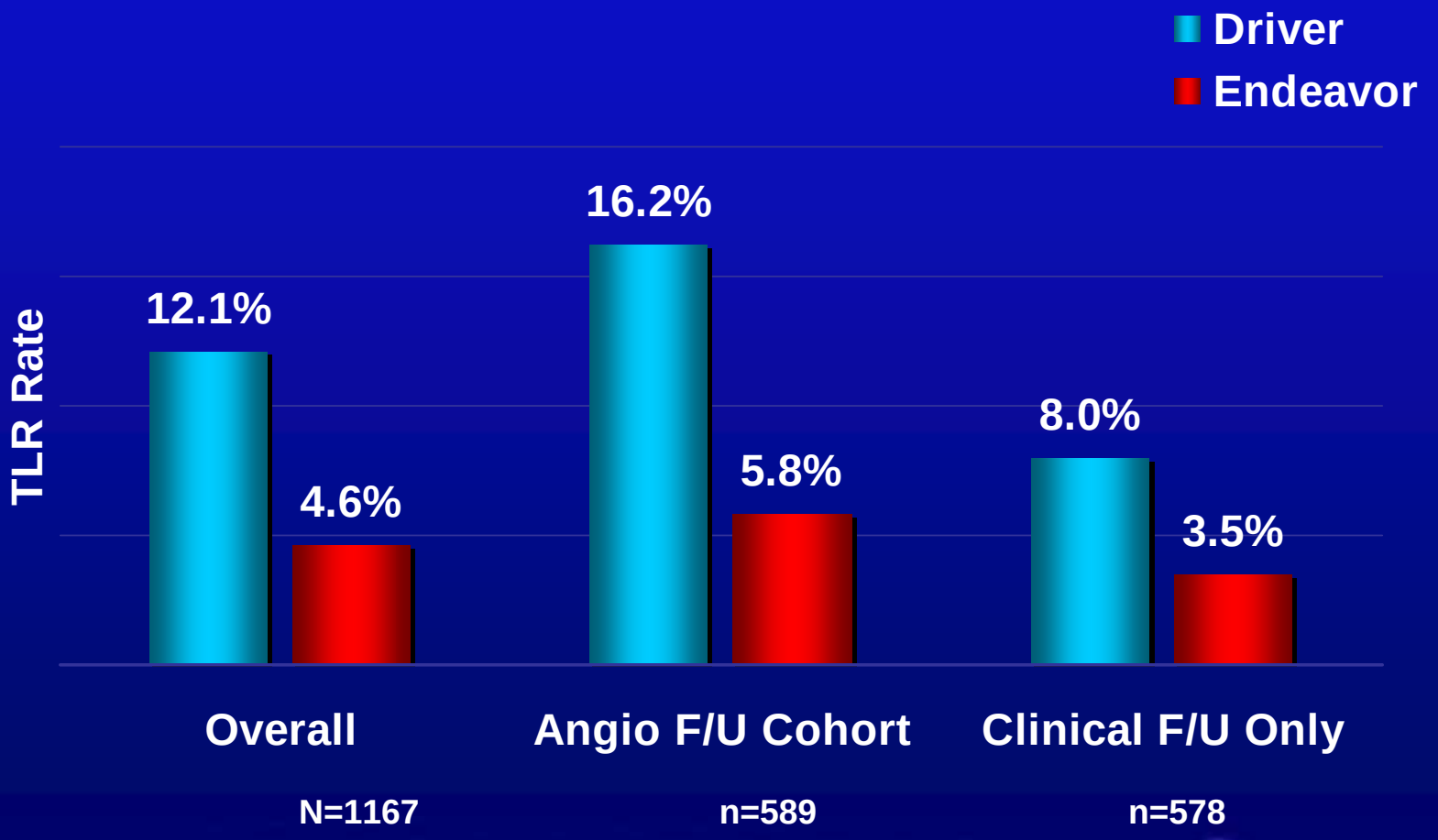
Target Lesion Revascularization

by Angiographic F/U Assignment



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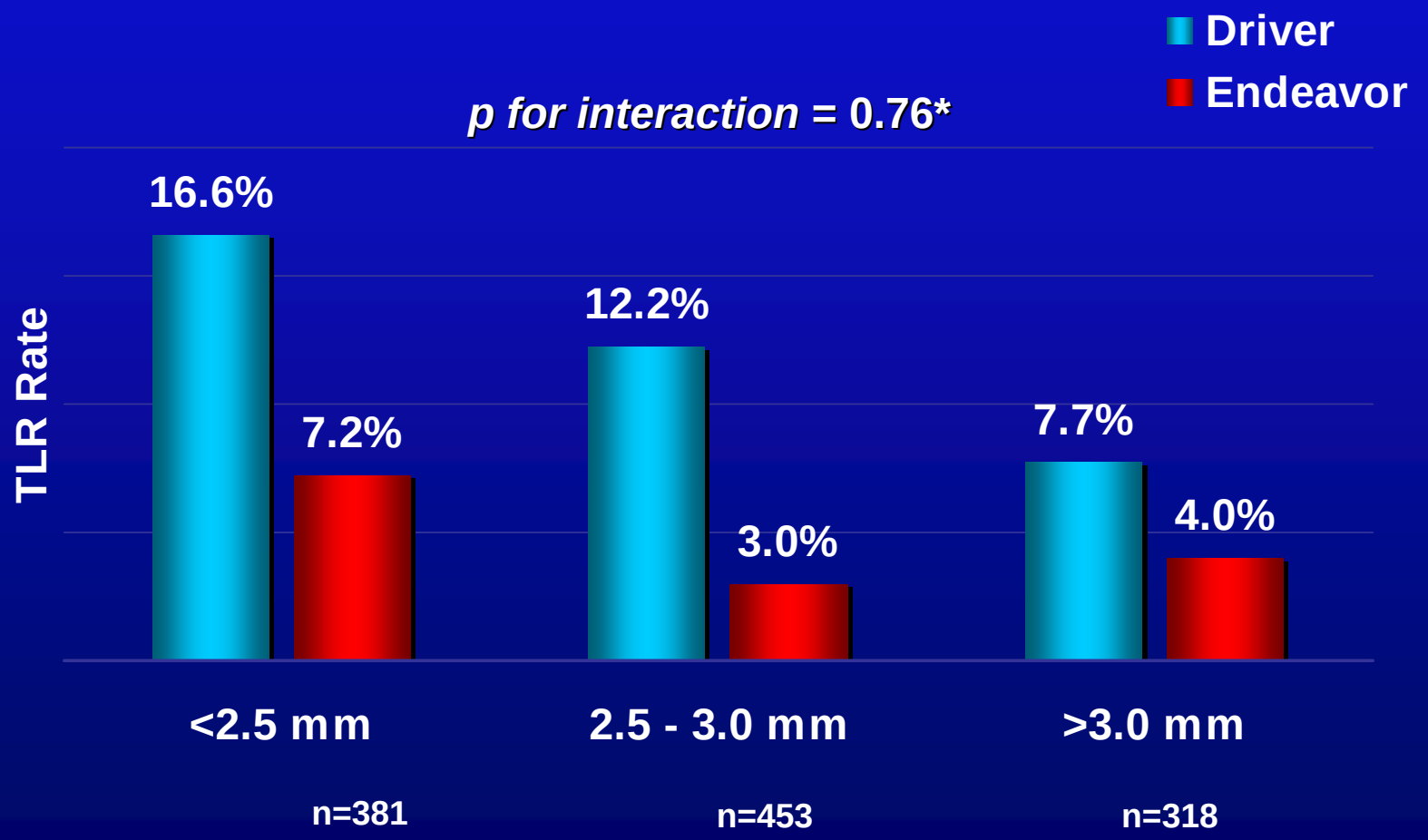
TLR by Vessel Size

Uniform Treatment Effect Across Vessel Diameters



*Non-significant interaction *p*-value demonstrates uniform treatment effect across different vessel sizes.

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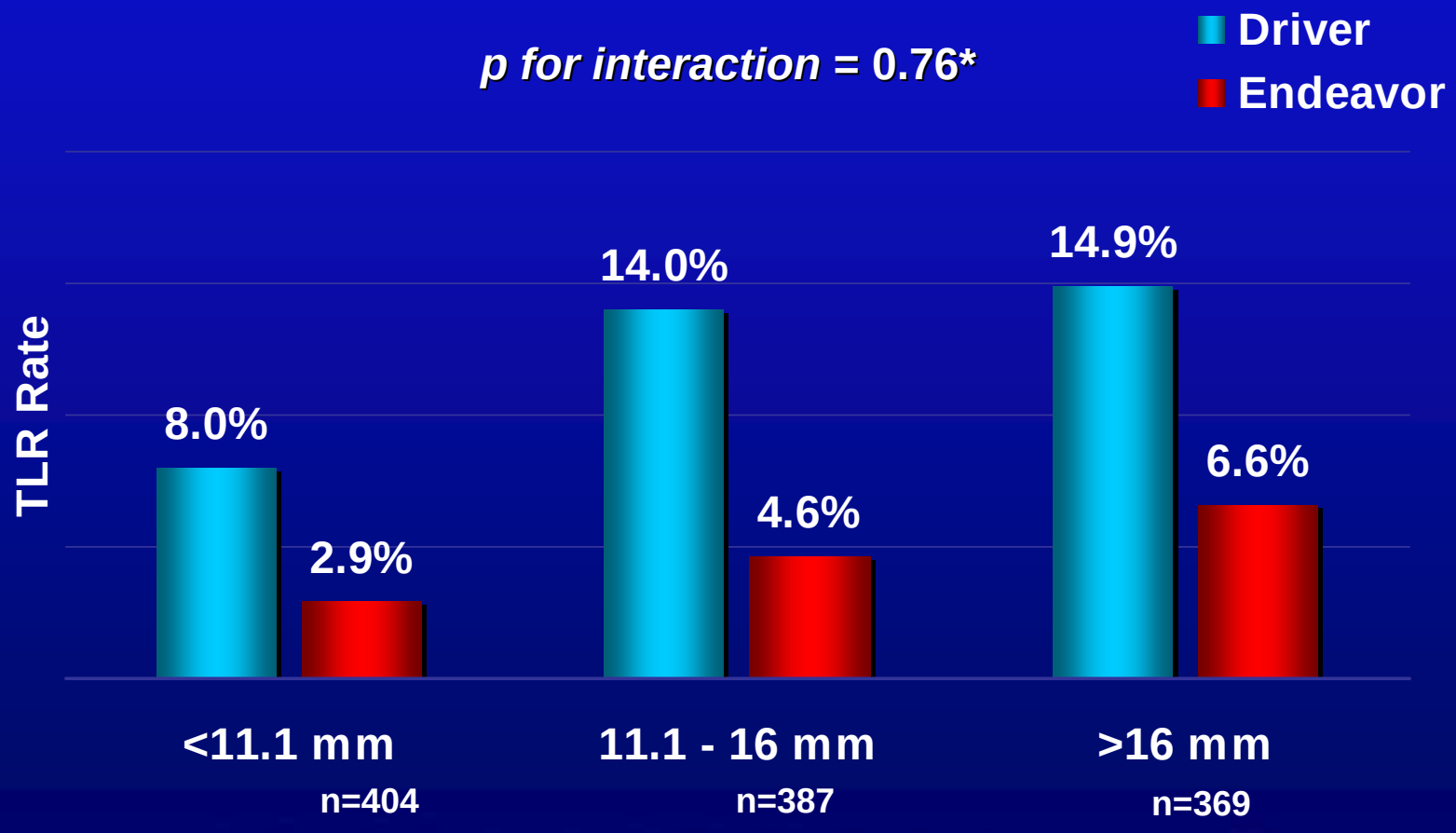
TLR by Lesion Length

Uniform Treatment Effect Across Lesion Lengths



*Non-significant interaction *p*-value demonstrates uniform treatment effect across different vessel sizes.

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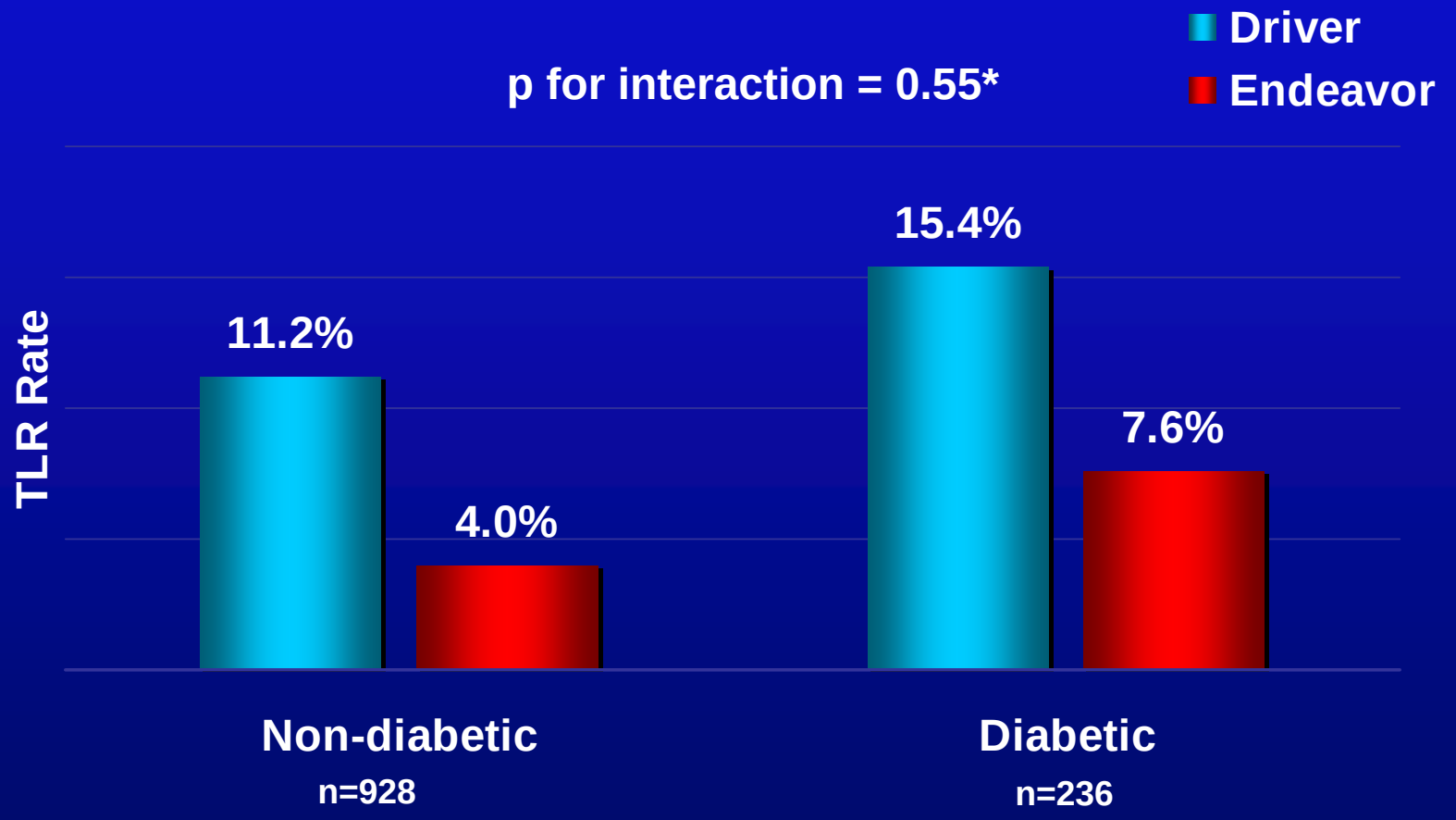
Diabetic Subset Analysis

Target Lesion Revascularization



* Non-significant interaction p-value demonstrates uniform treatment effect across diabetic and non-diabetic patients

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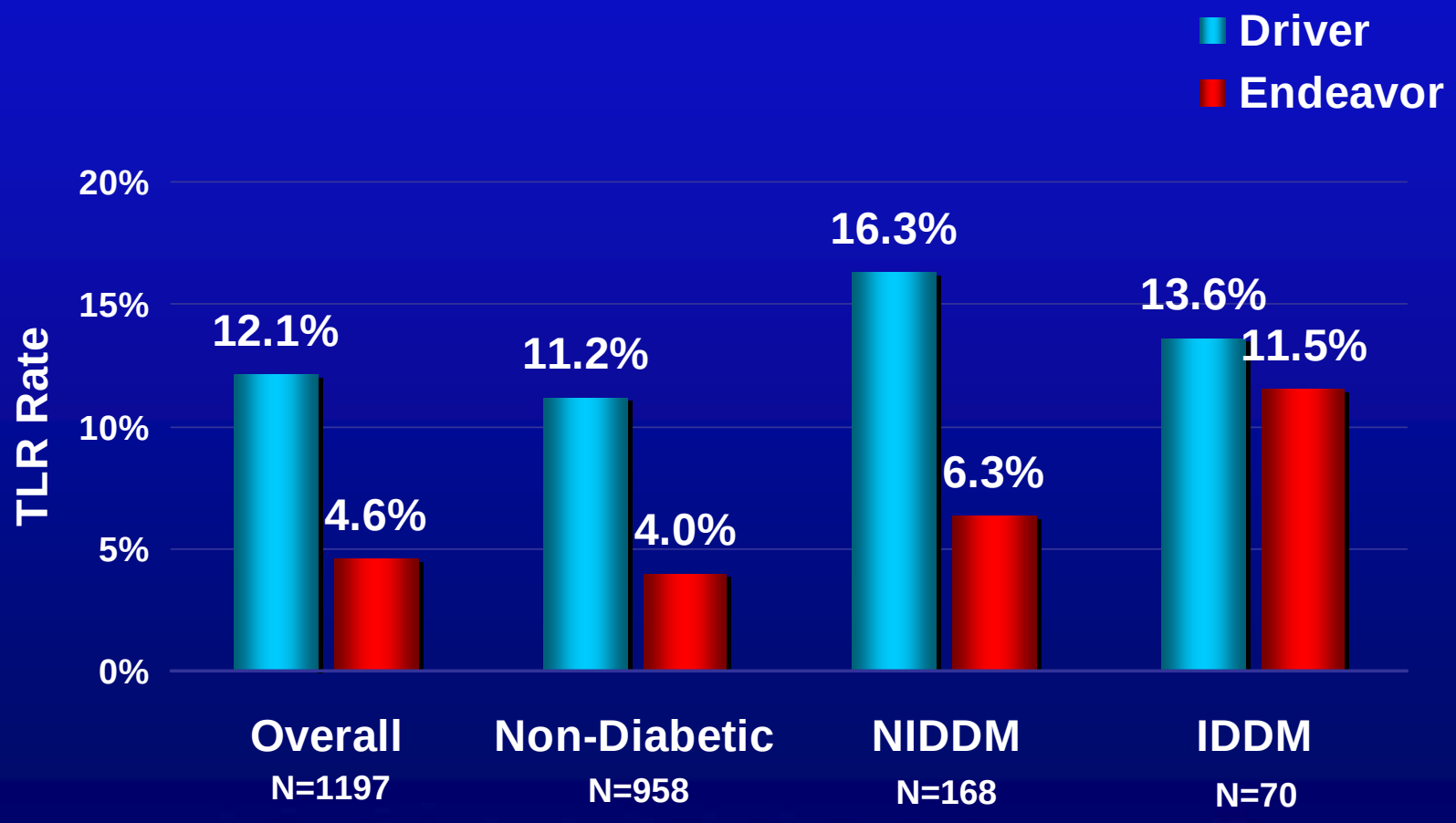
TLR Diabetic Subgroup

Uniform Treatment Effect in NIDDM



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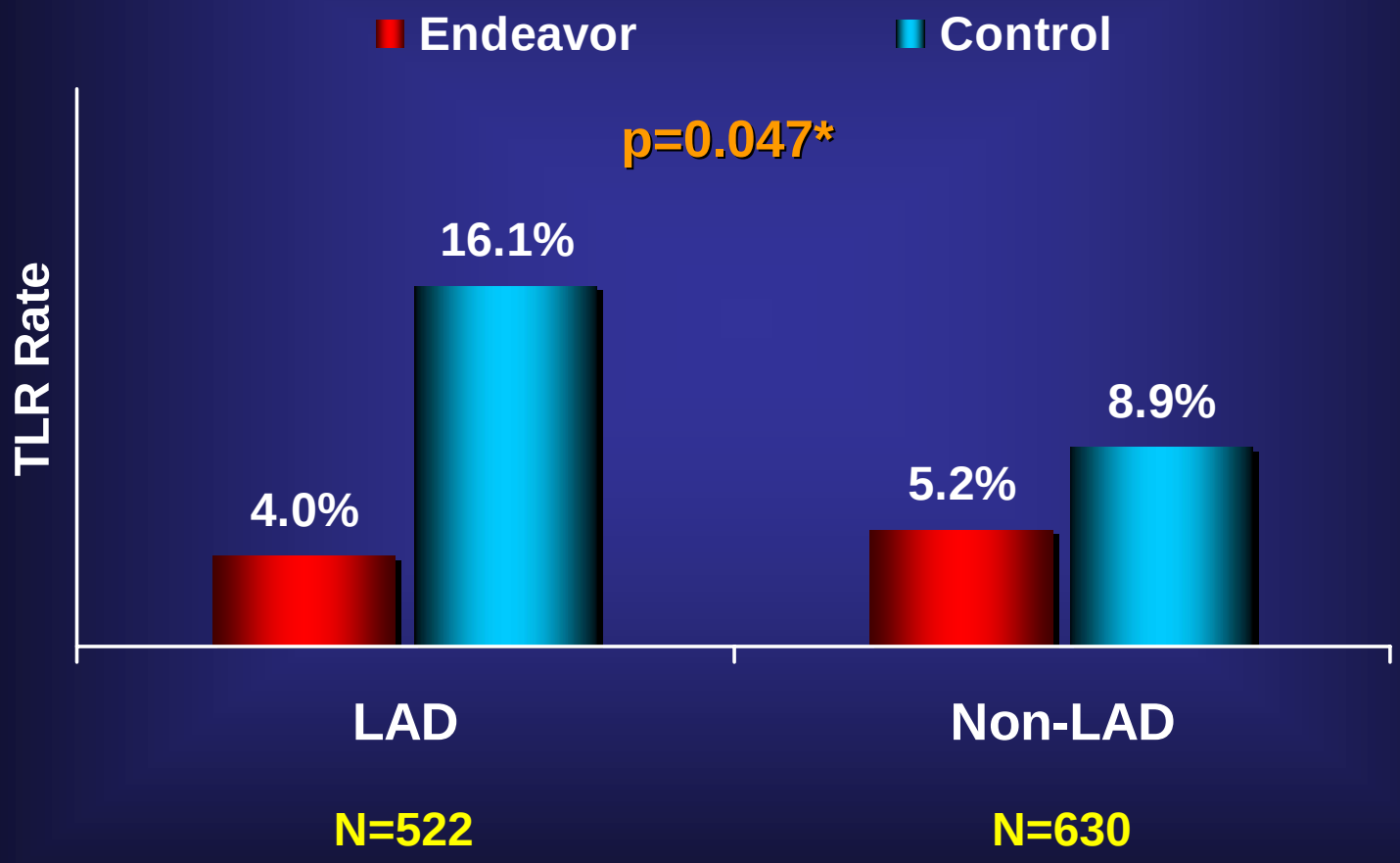
Target Lesion Revascularization

LAD Subset Analysis

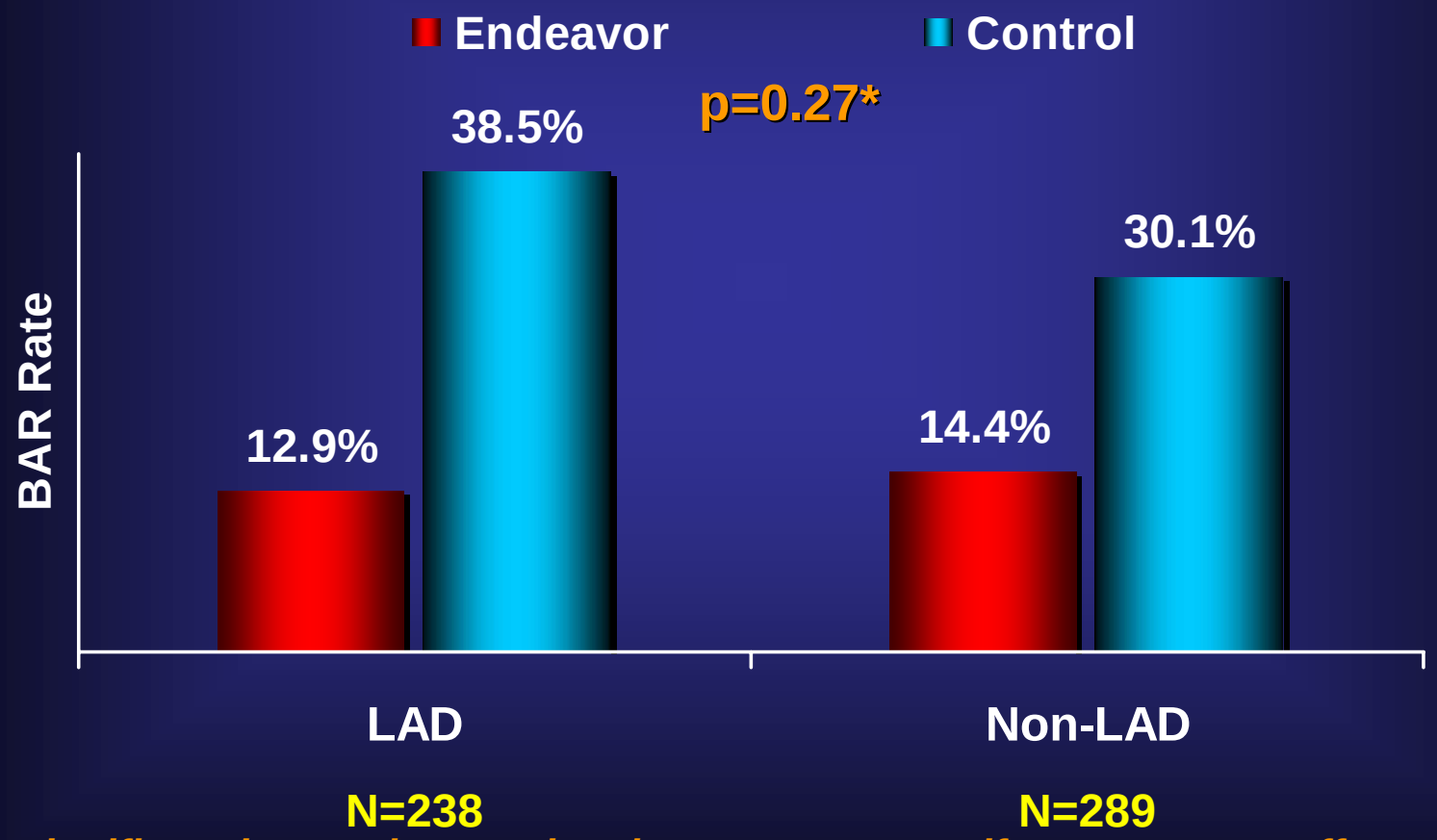


Borderline LAD and TLR interaction p-value demonstrates a mild differential treatment effect for Endeavor and LAD

ACC Late Breaking Trials, 6 March 2005

Binary Angiographic Restenosis

LAD Subset Analysis



** Non-significant interaction p-value demonstrates a uniform treatment effect by LAD vs. non LAD lesion location*

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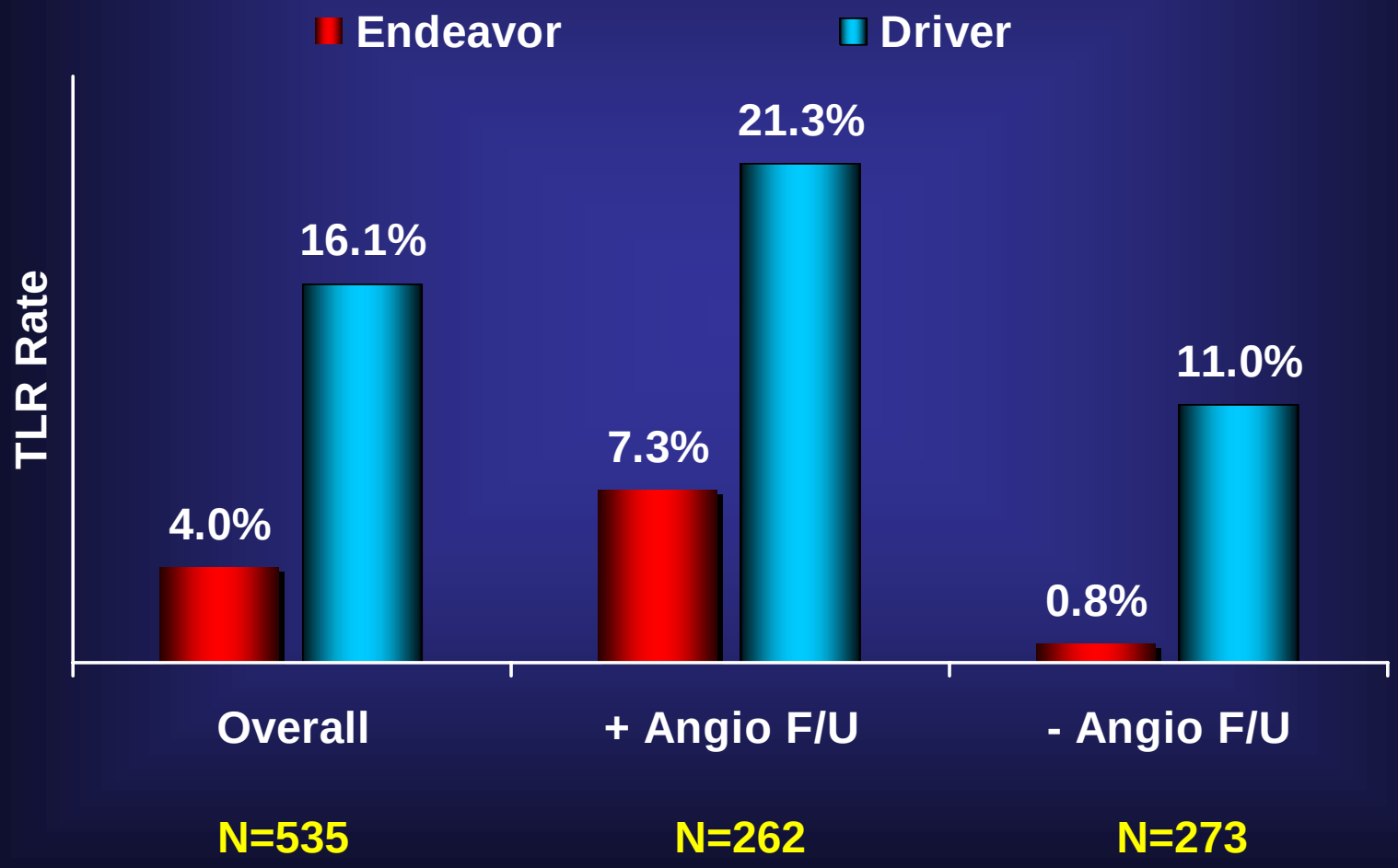
TLR by Angiographic Follow-up

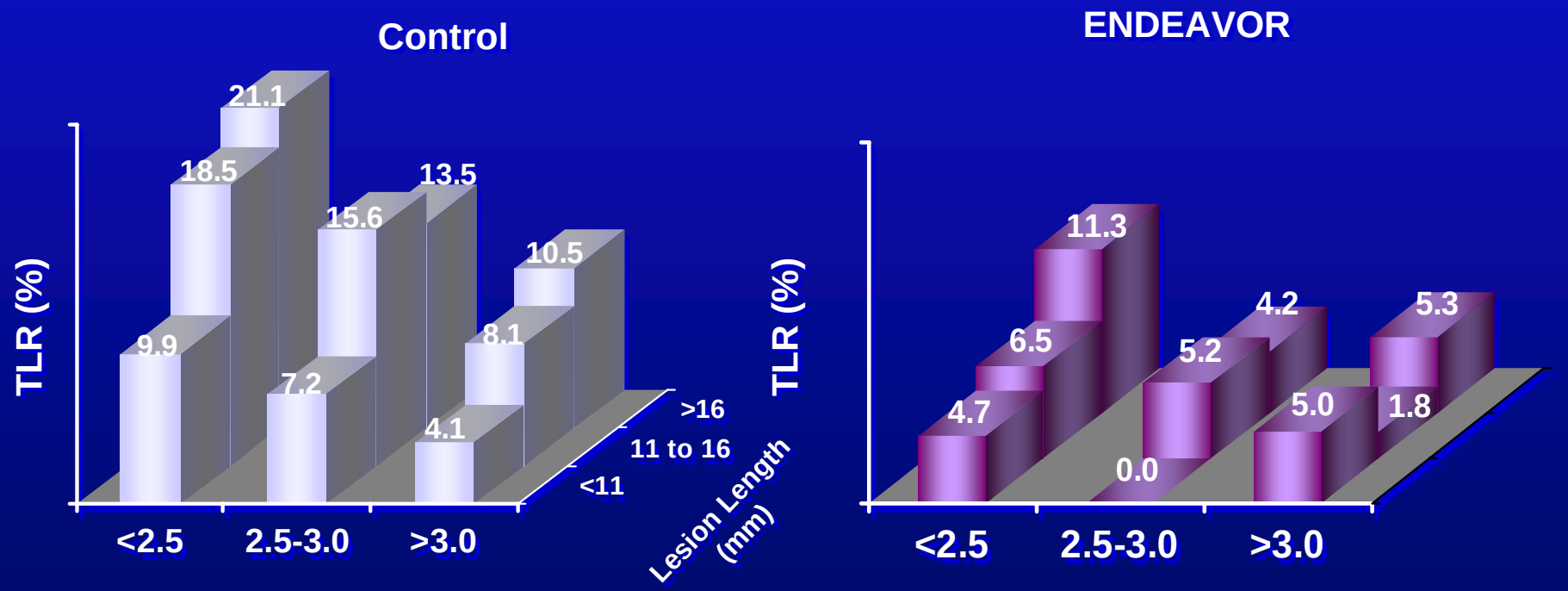
LAD Subset Analysis



ACC Late Breaking Trials, 6 March 2005

Target Lesion Revascularization

by Lesion Length, RVD, and Treatment



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Conclusion

- This pivotal trial provides the evidence that the Endeavor drug-eluting stent is safe and substantially reduces clinical restenosis compared to the Driver bare- metal stent.

- Taken together with the ease of use of the Driver stent platform,the results of the trial establish the Endeavor stent as a valuable treatment option for patients undergoing angioplasty with drug eluting-stents.

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