Polymer-Free Biolimus-Eluting Stent in Patients with High Risk for Bleeding

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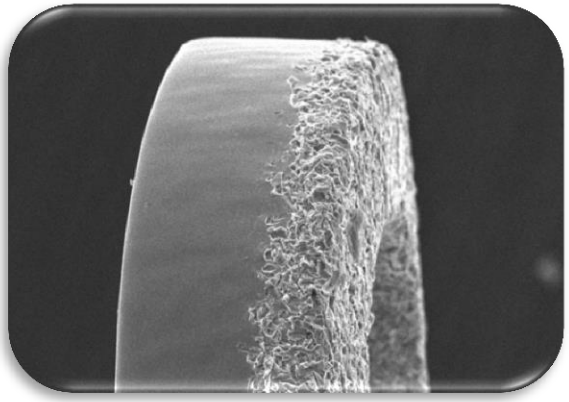
Delivering true innovation

BioFreedom™

- ✓ Ensures effective drug release kinetics without a polymer or carrier.
- ✓ A true drug-coated stent. BA9™ coated only on the abluminal surface

This innovation is made possible by the unique combination of two Biosensors' technologies:



A **stent surface micro-structured treatment** (SMS)

BA9™ BIOLIMUS A9™

Proprietary BA9 drug

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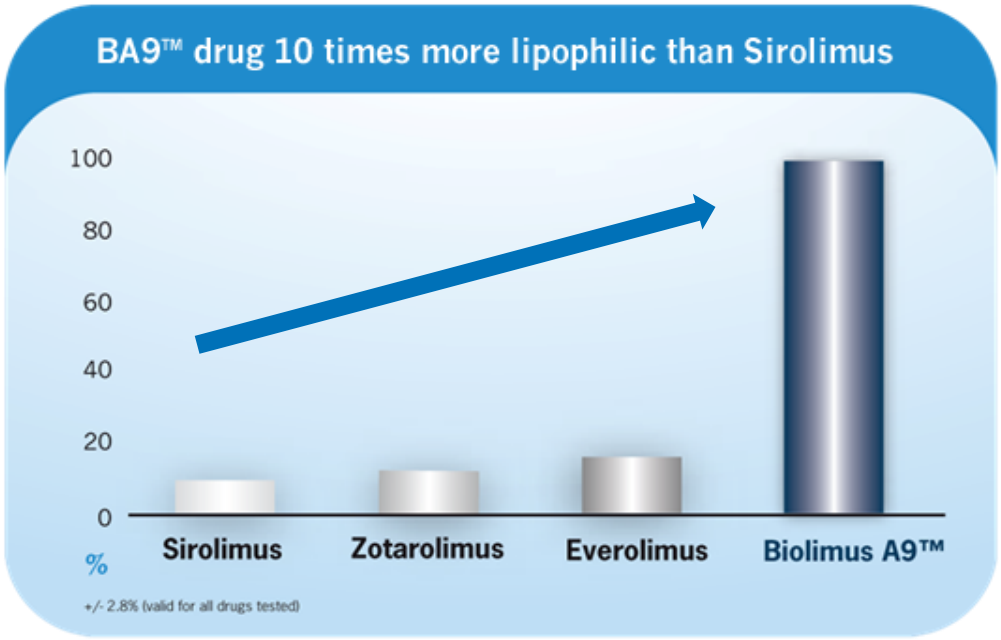
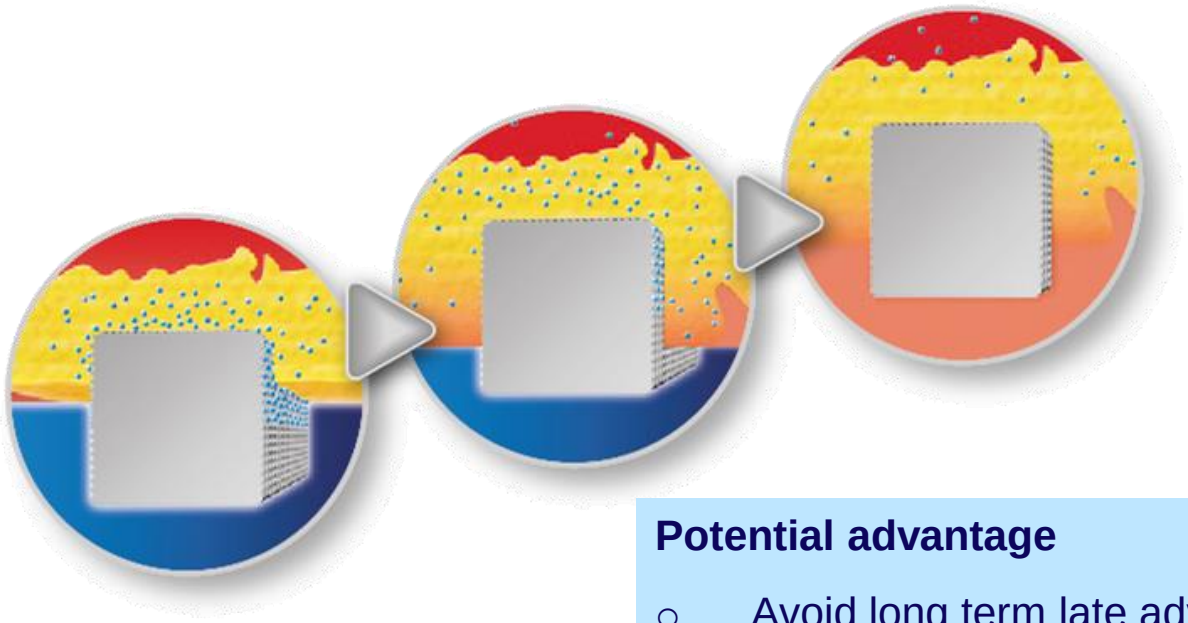
Lipophilicity comparison



- Highest lipophilicity of the common limus drugs[1]
- Minimizes systemic exposure and reduces the drug circulating in the bloodstream
- Due to high lipophilicity, the drug (BA9) is rapidly absorbed by local tissue

Hypothesis and Potential advantage

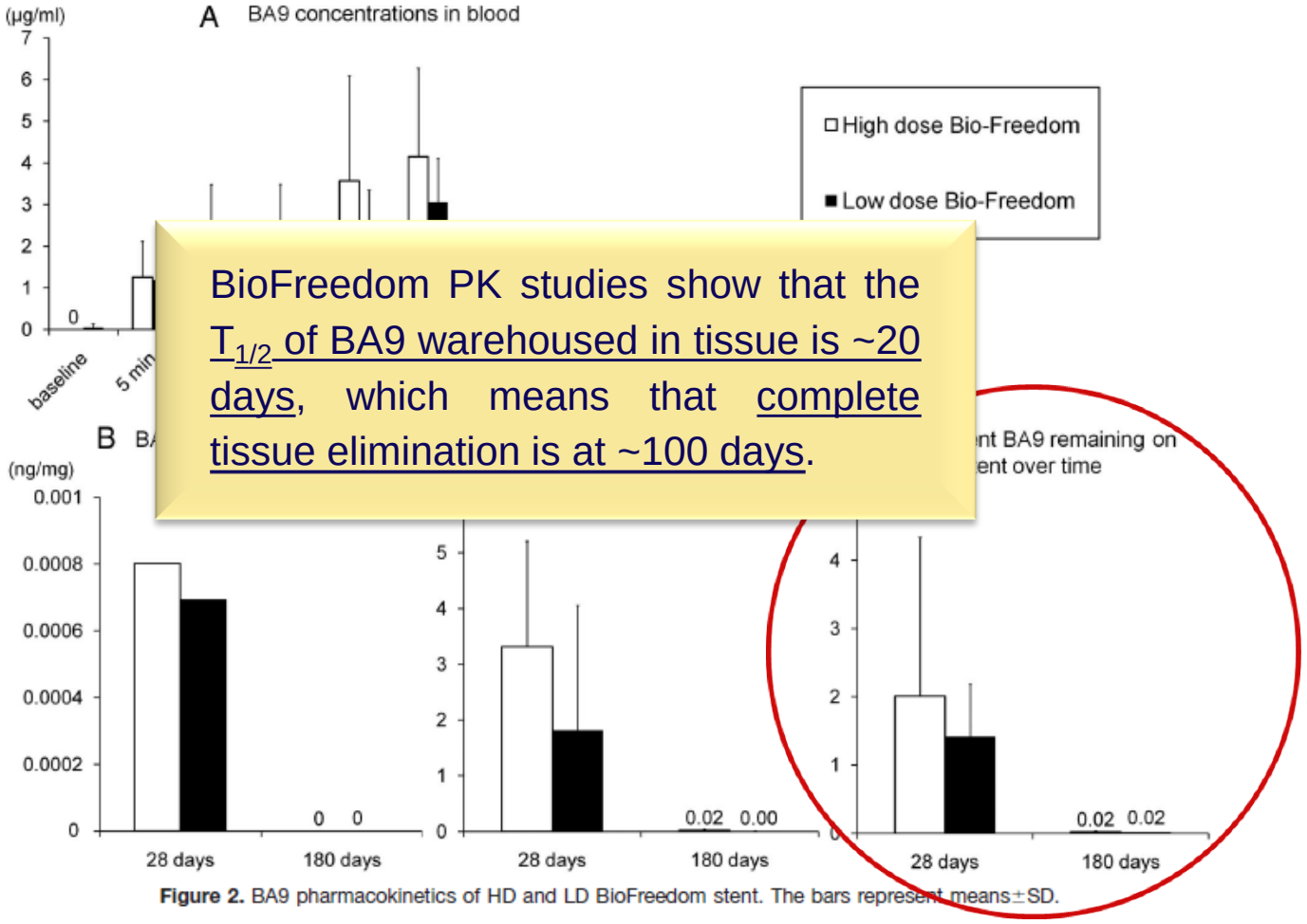


Hypothesis: Polymer-free drug release via porous-eluting stents may reduce late events caused by polymer stent coatings.

Potential advantage

- Avoid long term late adverse effects that might be attributable to durable polymers
- Improved surface integrity since there is no polymer to be sheared or peeled away from the stent struts
- Potential for shorter DAPT regimes

Vascular Transfer and Residence Time



BioFreedom PK studies show that the $T_{1/2}$ of BA9 warehoused in tissue is ~20 days, which means that complete tissue elimination is at ~100 days.

Figure 2. BA9 pharmacokinetics of HD and LD BioFreedom stent. The bars represent means±SD.

Five year and Final Report of BioFreedom First-In-Man, a Randomized Trial comparing Polymer-Free BioFreedom™ stents with Durable Polymer Taxus Liberté™ Stents

Presented at TCT 2014

On behalf of the BioFreedom FIM investigators: Eberhard Grube, Ralf Mueller, Gerhard Schuler, Karl-Eugen Hauptmann, Joachim Schofer, Carlo Di Mario

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BioFreedom FIM Trial Design

Symptomatic, ischemic heart disease
Native coronary artery ≥ 2.25 mm and ≤ 3.0 mm, Lesion length ≤ 14 mm
Randomization 1:1:1 (N=182)

BioFreedom™ Standard Dose 15.6 µg/mm N=60	BioFreedom™ Low Dose 7.8u µg/mm N=62	Taxus® Liberté® Paclitaxel-Eluting St. N=60

Clinical Follow-up

30 d | 4 mo | 12 mo | 2 yrs | 3 yrs | 4 yrs | 5 yrs

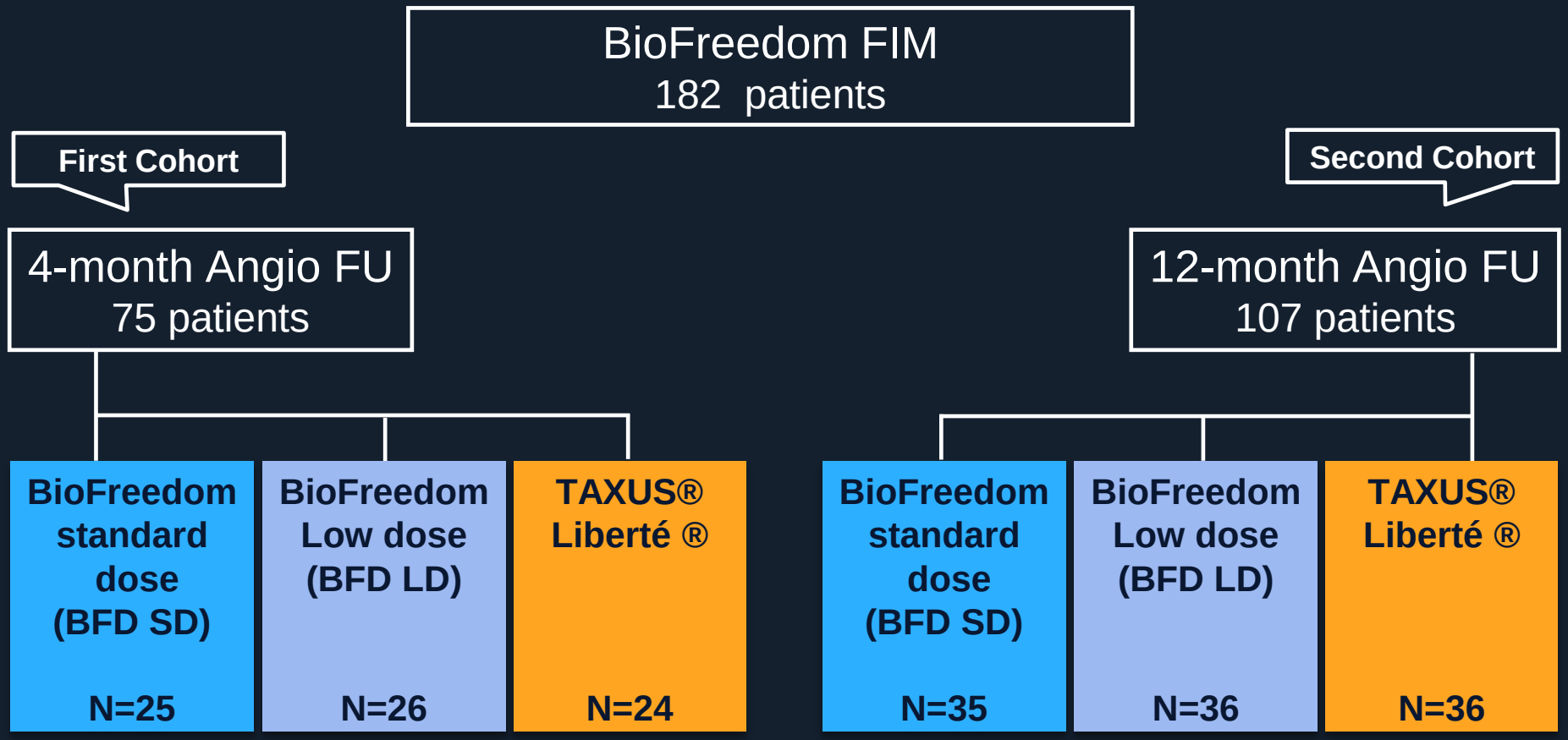
Angiographic and IUVS Follow-up

Primary Endpoint: In-stent Late Lumen Loss (LLL) at 12 months[2]

Key 2° Endpoints:
- In-stent LLL at 4-months[1]
- MACE*/ST rate at 30 days, 4 months, and 1, 2, 3, 4, 5 years
- Clinically-driven TLR, TVR and TVF at 4 and 12 months, and 2, 3, 4, 5 yrs
- In-stent/In-segment binary restenosis at 4 months[1]/12 months[2]
- In-stent/In-segment Minimum Lumen Diameter (MLD) at 4 months[1]/12 months[2]
- In-stent, proximal and distal LLL at 4 months[1]/12 months[2]
- Neointimal hyperplasia volume at 4 months[1]/12 months[2] as measured by IVUS
- BA9 concentrations at pre-/post-procedure, discharge and 30 days / 4 months

MACE defined as Death, MI, emergent bypass surgery or TLR
DAPT recommended for a minimum of 6 months

BioFreedom FIM Trial Design



Enrollment Period Sept 2008 – Jan 2009

Enrollment Period Jan 2009 – Jun 2009

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Baseline Clinical Demographics

All Patients – 1st and 2nd Cohorts (N=182)

Variable	BFD SD N = 60	BFD LD N = 62	TAXUS N = 60
Age (mean ± SD)	68.6 ± 9.0	65.0 ± 9.4	67.9 ± 8.0
Male (%)	67	76	67
Diabetes Mellitus (%)	28	29	25
Current Smoker (%)	17	20	12
Hypertension (%)	90	81	85
Hypercholesterolemia (%)	68	74	75
Previous MI (%)	20	21	18
Previous PCI (%)	32	44	46
Unstable Angina (%)	12	13	7

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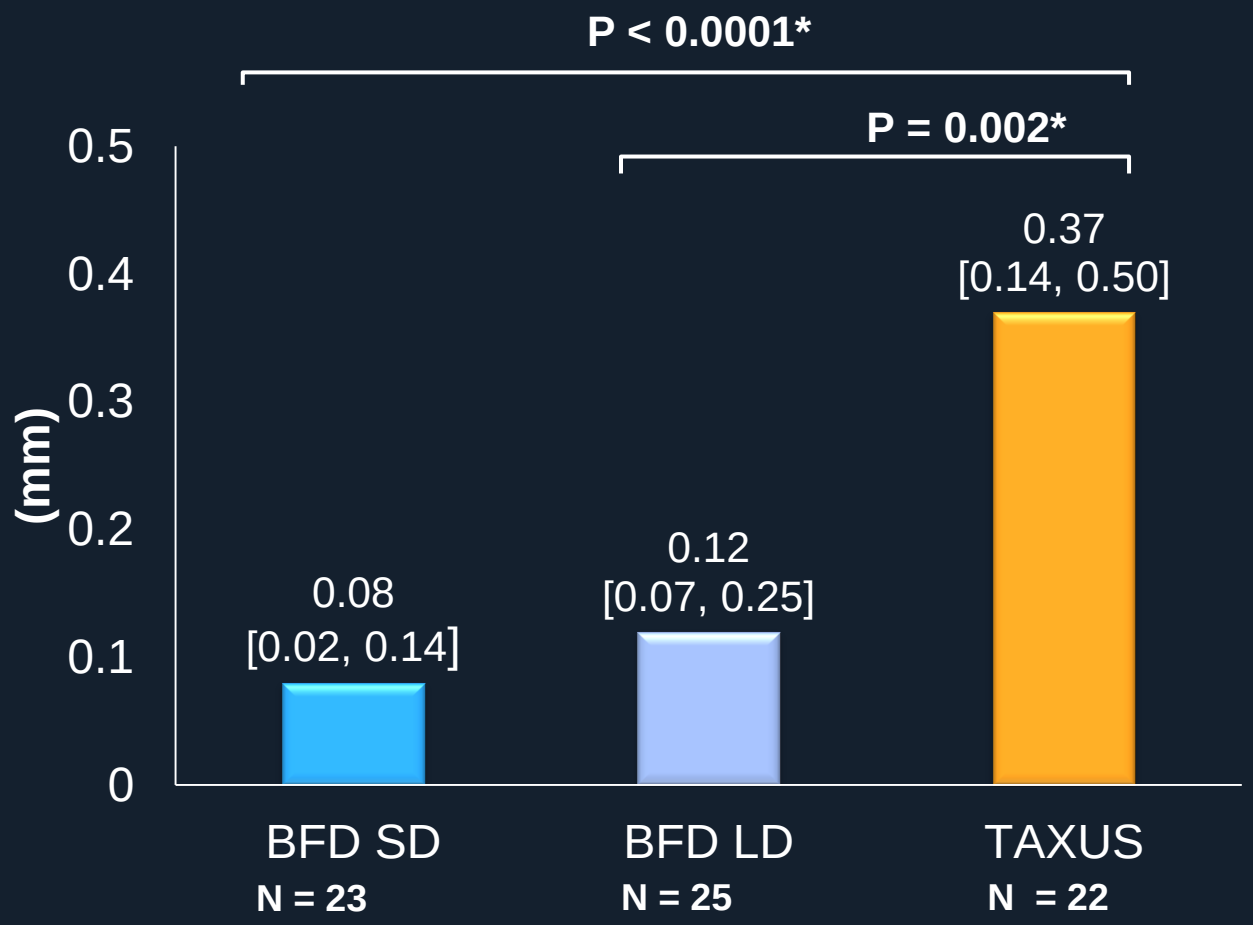
In-Stent LLL at 4-month Follow-up

1st Cohort – Secondary Endpoint



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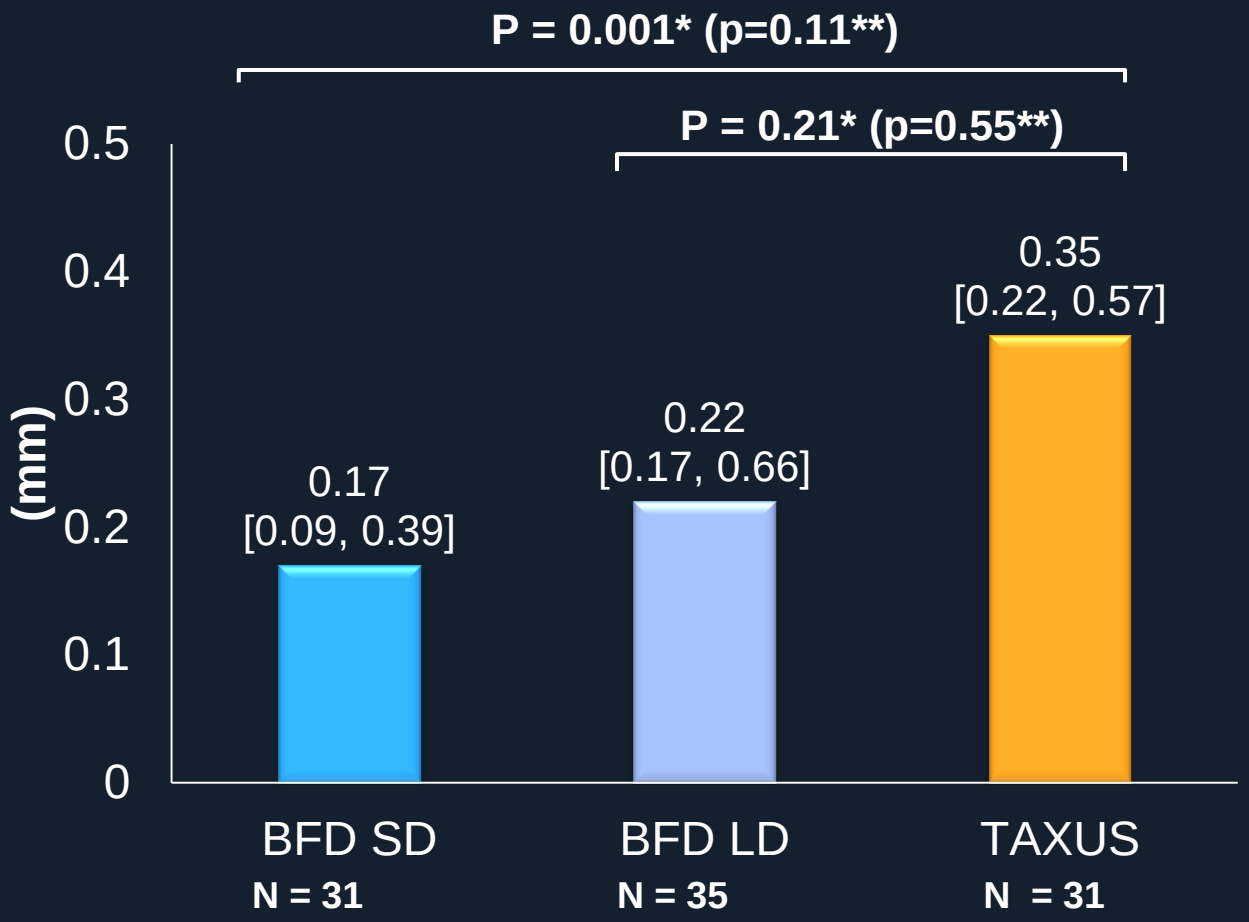
In-Stent LLL at 12-month Follow-up

2nd Cohort – Primary Endpoint



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60-month Clinical Outcomes

All Patients – 1st and 2nd Cohorts (95.8%)

Event	BFD SD N = 60	BFD LD N = 62	TAXUS N = 60
MACE (All Death, MI, Emergent Bypass or TLR)	14 (23.8%)	16 (26.4%)	12 (20.3%)
All Death	5 (8.5%)	7 (11.6%)	4 (6.9%)
Cardiac Death	3 (5.2%)	2 (3.6%)	0 (0.0%)
MI	3 (5.3%)	2 (3.3%)	2 (3.5%)
Q Wave MI	0 (0.0%)	0 (0.0%)	1 (1.8%)
Non-Q Wave MI	3 (5.3%)	2 (3.3%)	1 (1.7%)
Emergent Bypass	0(0.0%)	0(0.0%)	0(0.0%)
TLR	6 (10.8%)	9(15.1%)	7(11.9%)
Definite / Probable Stent Thrombosis (ARC)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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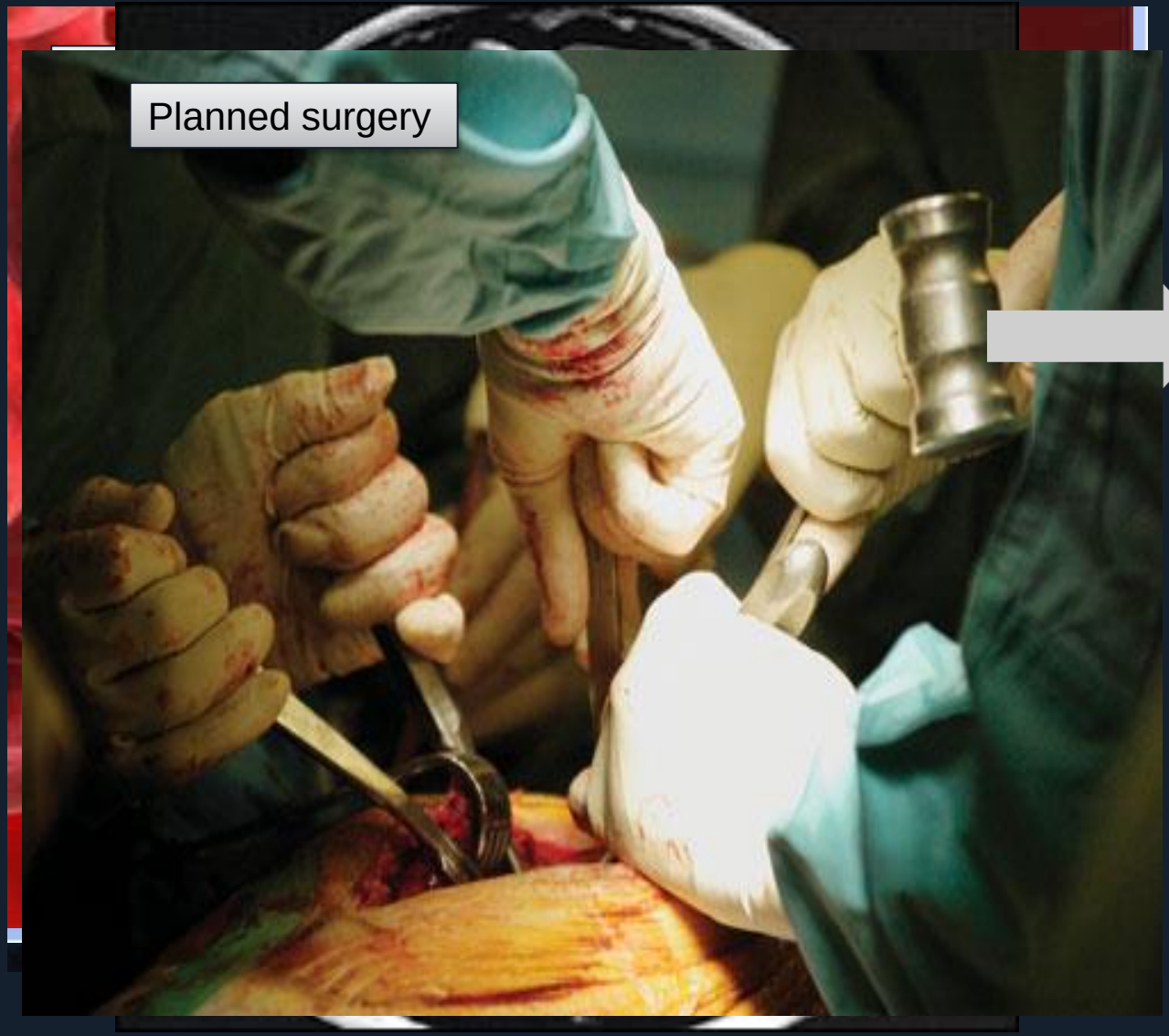
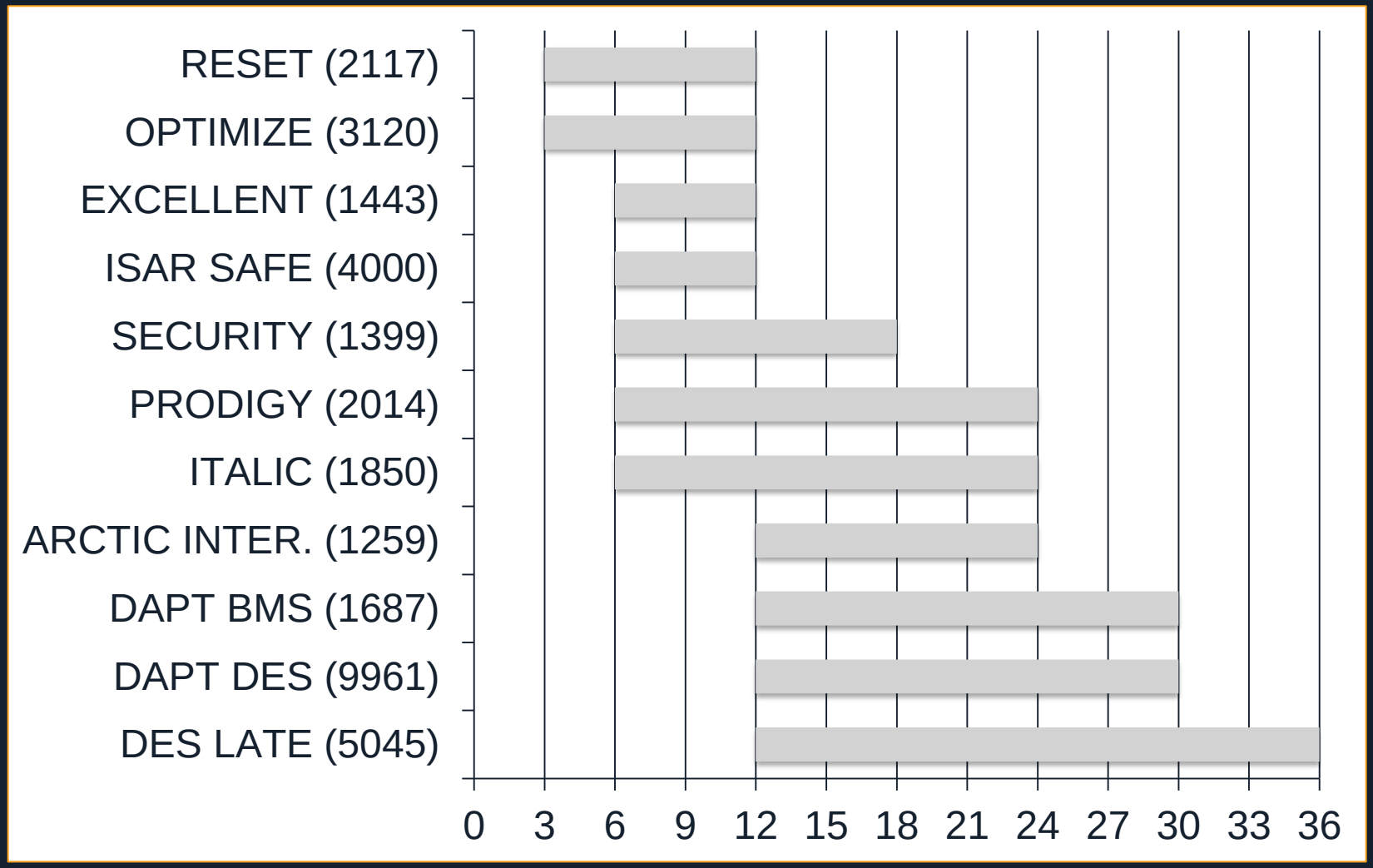
Needs for DES in Patients at High Risk of Bleeding: A Forgotten Population In DES Trials

Patients at High Bleeding Risk (HBR)



BMS

DAPT duration after stenting

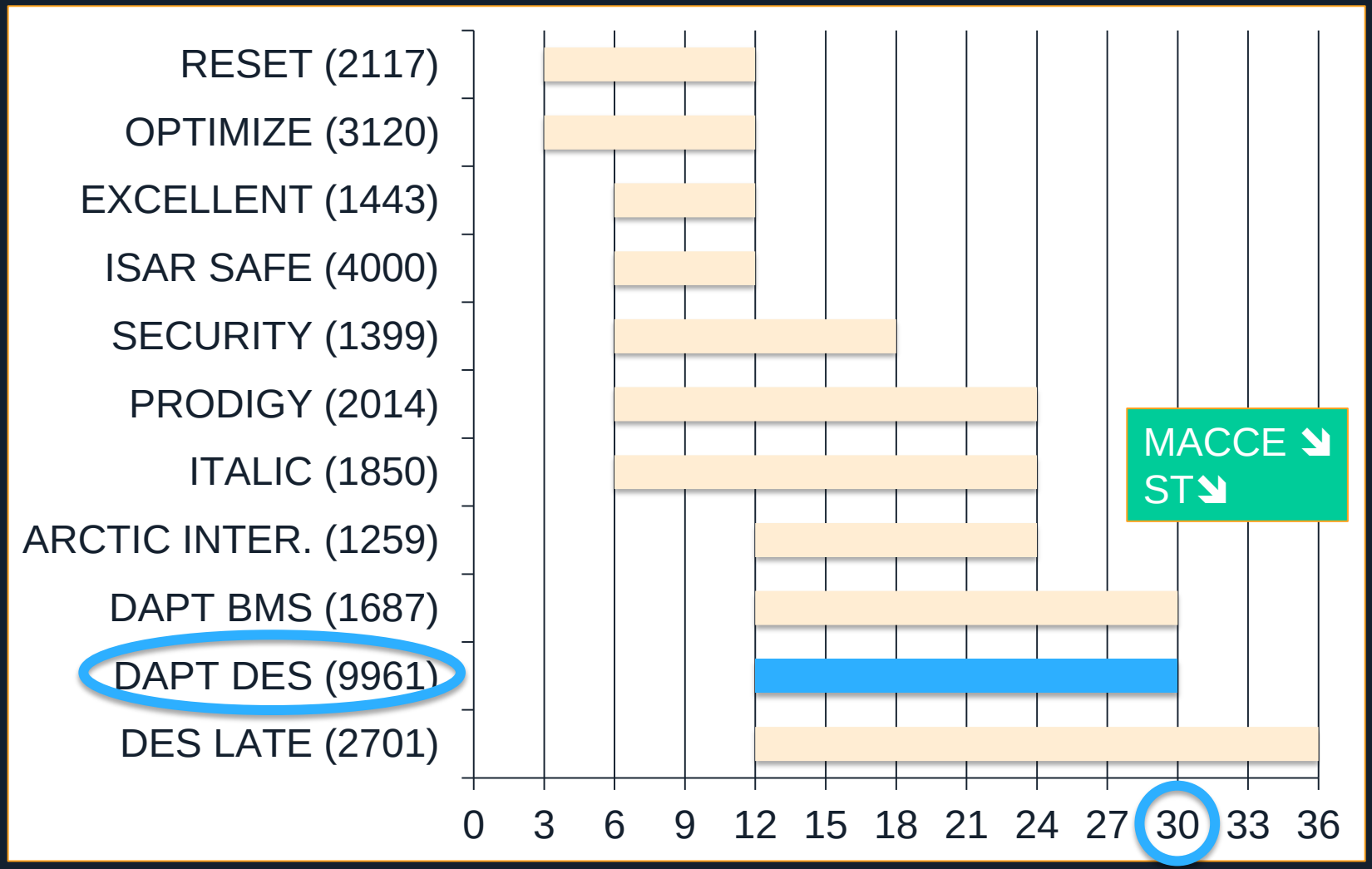


11 trials & > 30,000 patients

15

Courtesy of P. Urban

DAPT duration after stenting

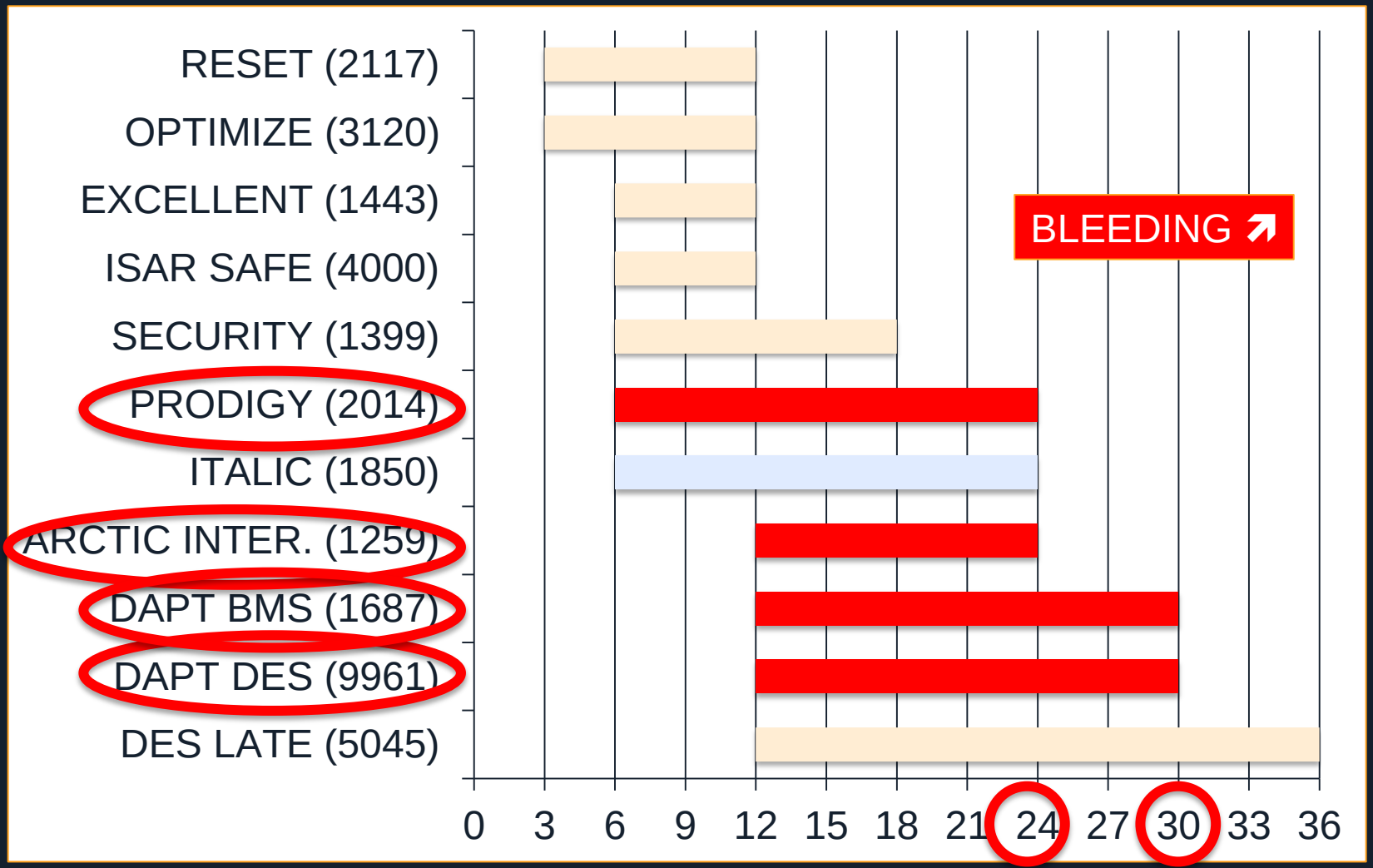


11 trials & > 30,000 patients

16

Courtesy of P. Urban

DAPT duration after stenting



11 trials & > 30,000 patients

17

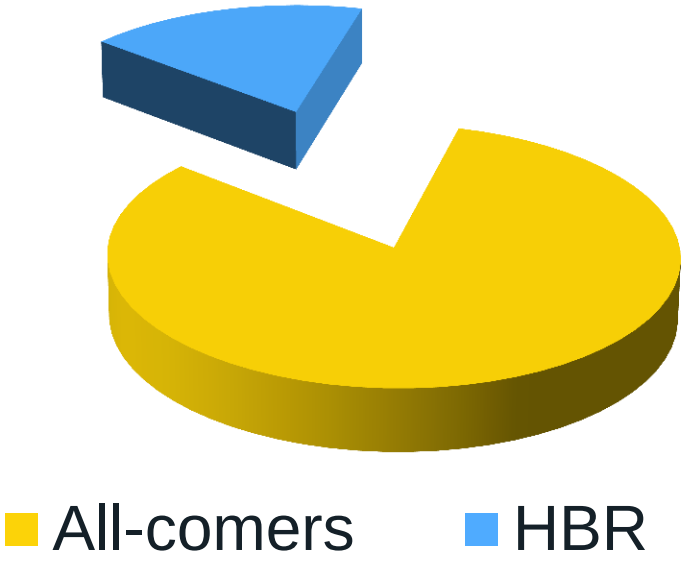
Courtesy of P. Urban

LEADERS FREE

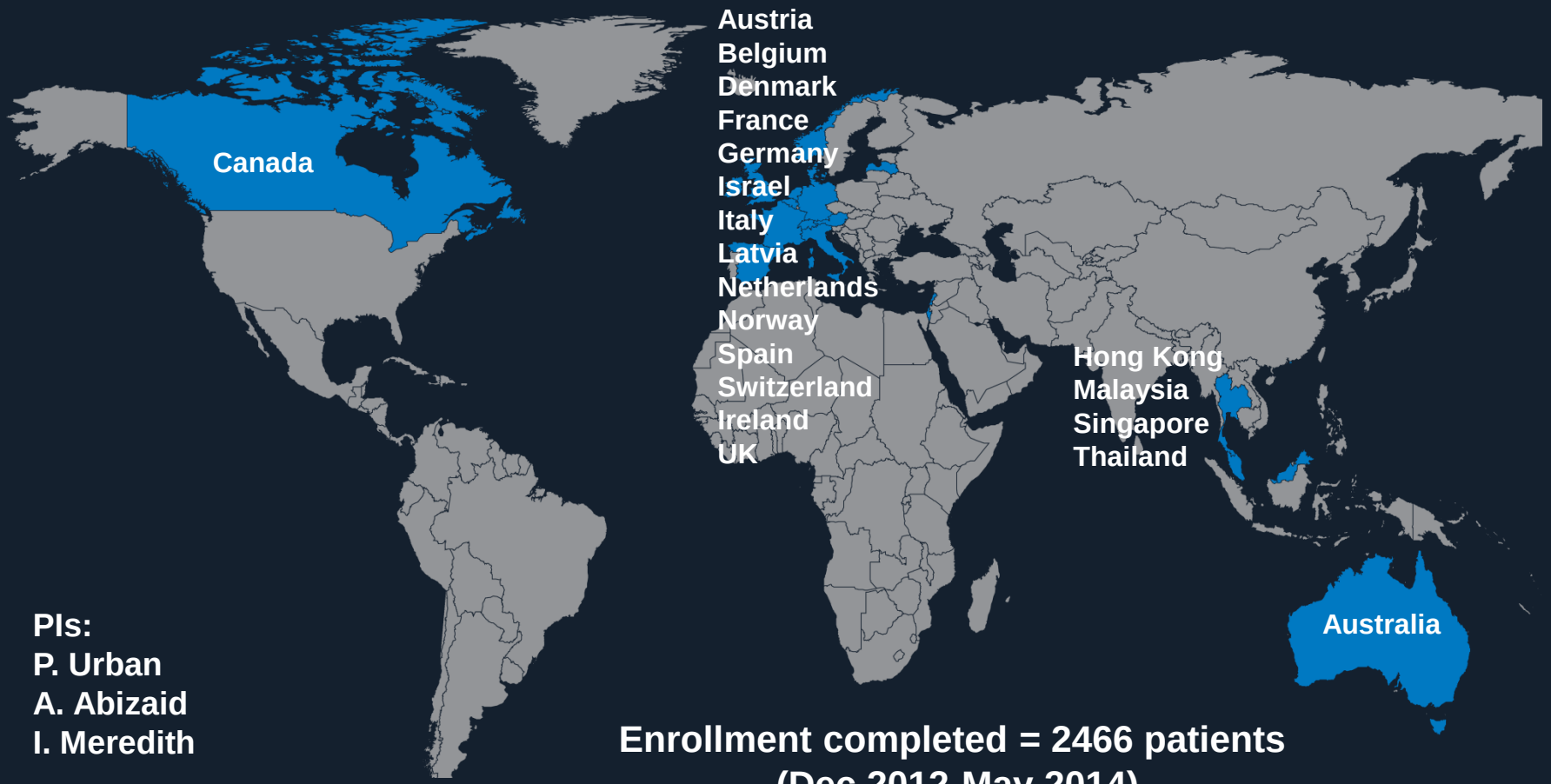
Biolimus-Coated vs. Bare-Metal Coronary Stents in High Bleeding Risk Patients

High Bleeding Risk Patients (HBR)

- Mostly excluded from device trials
- Never specifically studied
- Current guideline recommendations:
  - BMS + one month DAPT
  - DES + “shortened” DAPT



Participating Countries

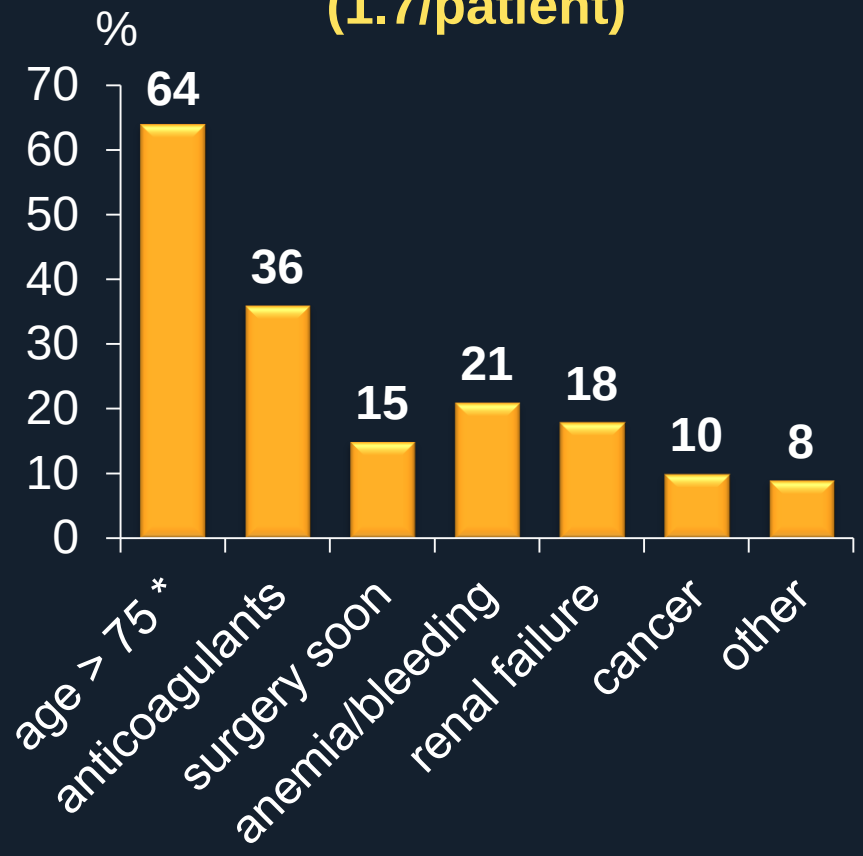


PIs:
P. Urban
A. Abizaid
I. Meredith

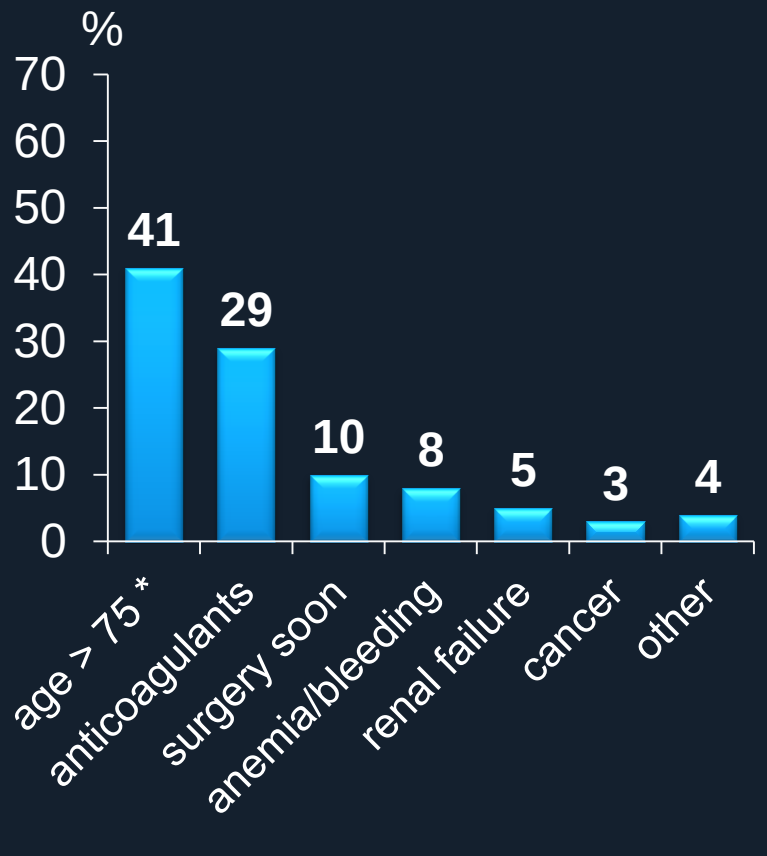
Enrollment completed = 2466 patients
(Dec 2012-May 2014)

Inclusion Criteria Applied (n=2466)
(i.e. Reasons for High Bleeding Risk)

All inclusion criteria (1.7/patient)

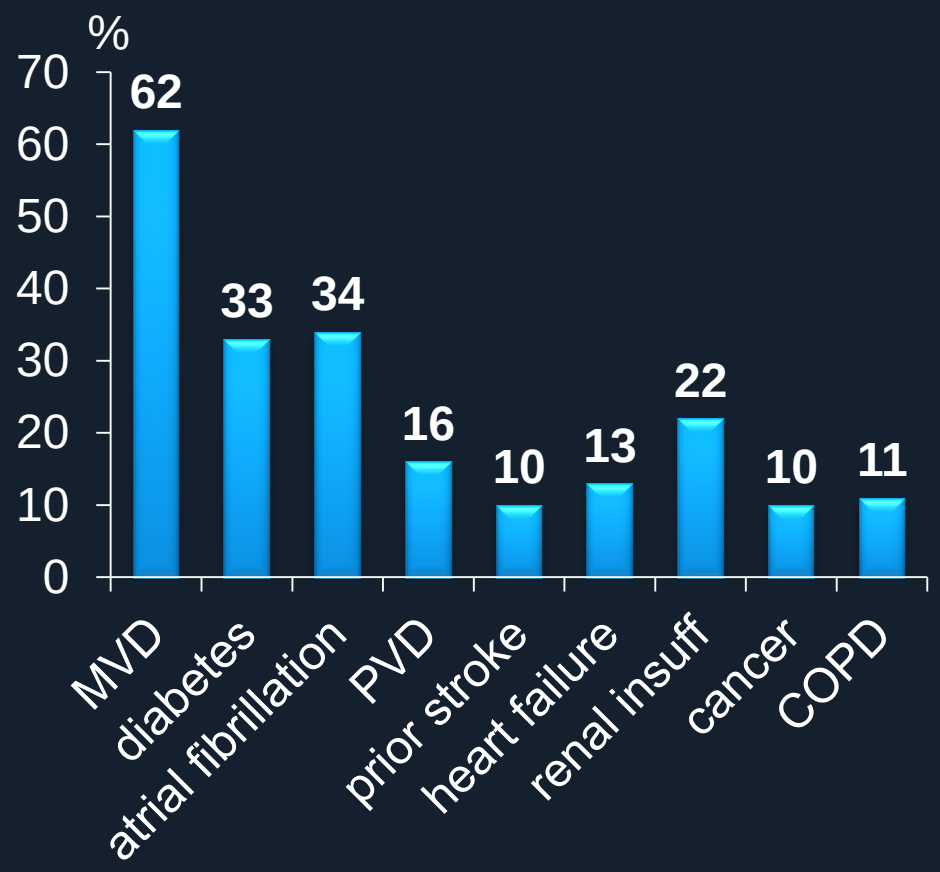


Single main inclusion criterion



Baseline Demographics (n=2466)

- 68 centers in Europe, Asia, Australia and Canada
- Mean age 76±9 years
- 70% male
- Presentation:
  - 58% stable angina
  - 15% unstable angina
  - 23% NSTEMI
  - 4% STEMI



Urban P., poster presentation TCT2014
Data are currently only partially monitored and subject to changes prior to definitive reporting

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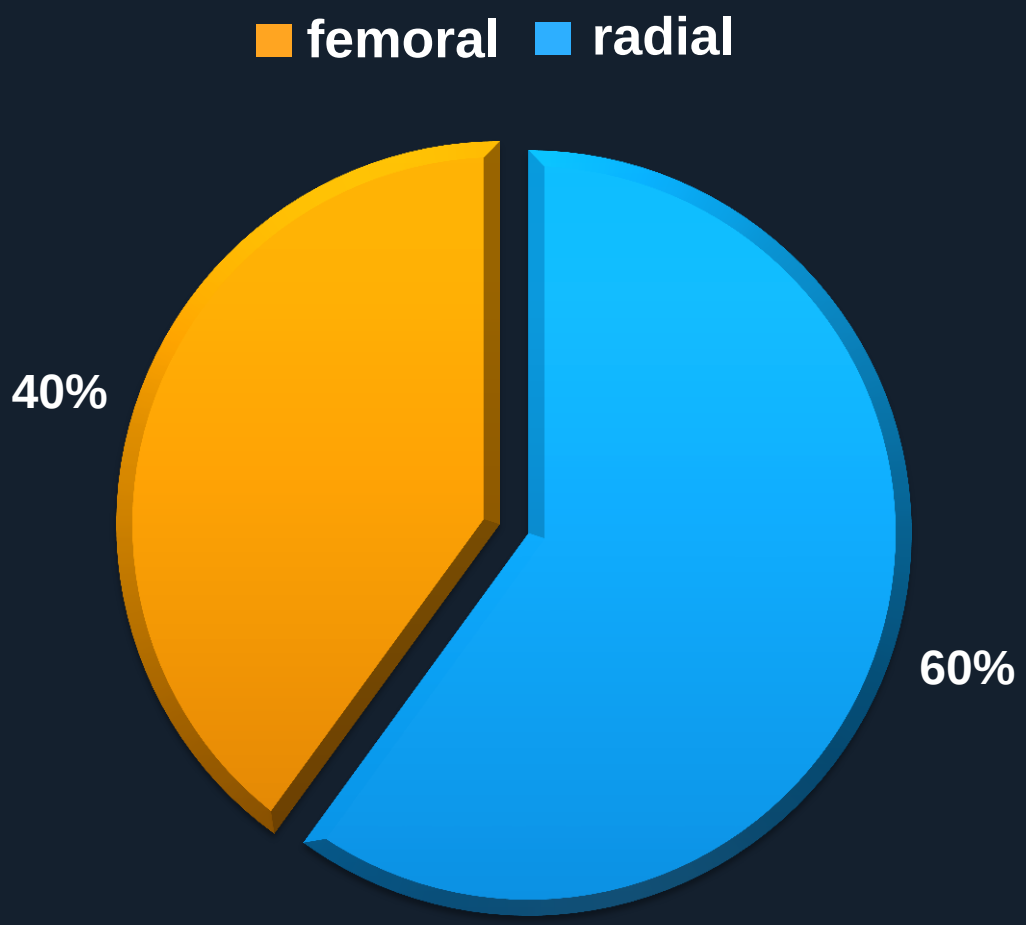
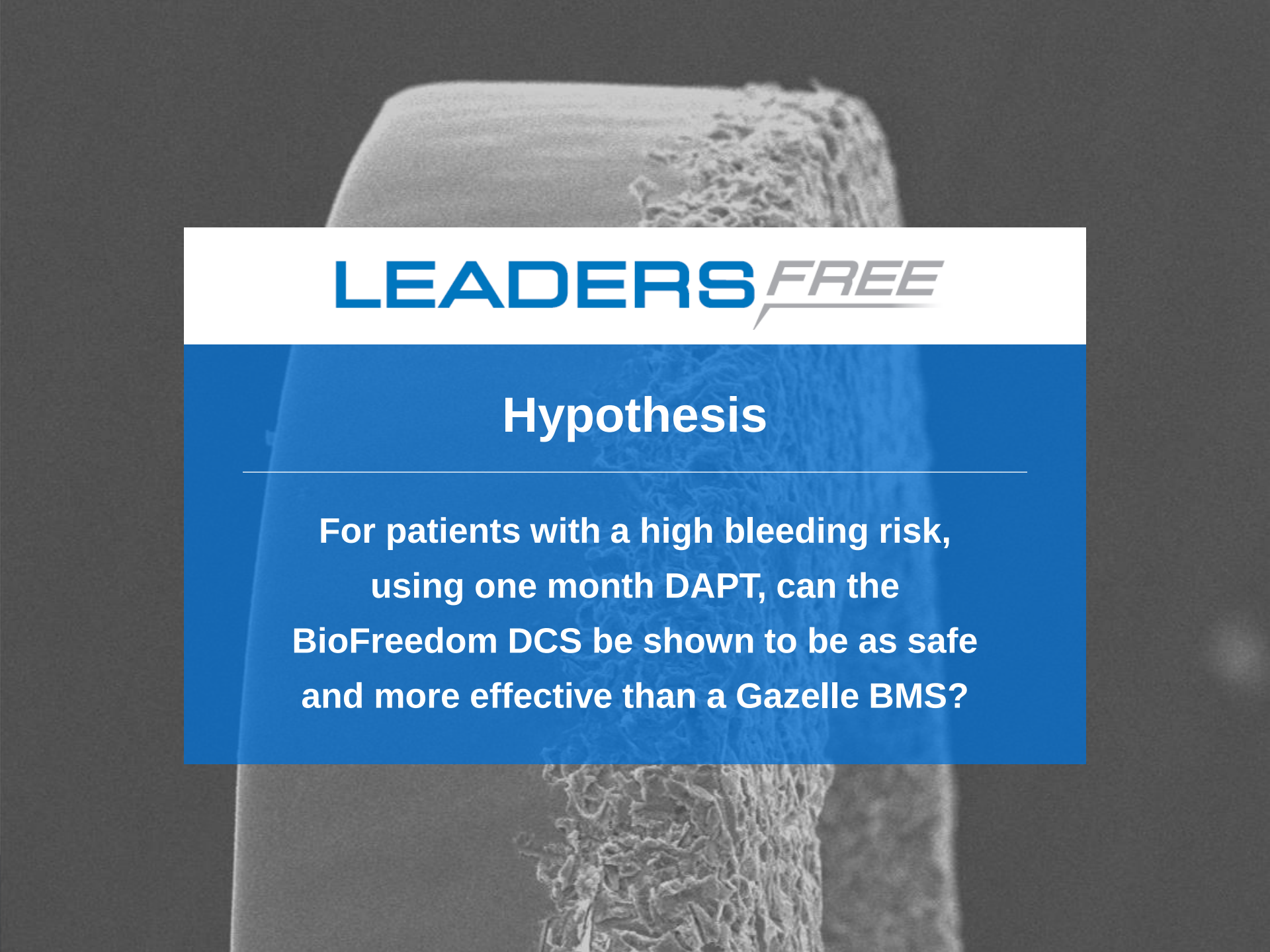
Vascular Access





LEADERS FREE

Hypothesis

For patients with a high bleeding risk, using one month DAPT, can the BioFreedom DCS be shown to be as safe and more effective than a Gazelle BMS?

LEADERS FREE Trial Design

Prospective, multi-center, multi-national, double blinded randomized trial
High Bleeding Risk PCI population
(ACS + Elective stable patients)
PI: P. Urban

2466 patients in 68 centers worldwide

BioFreedom™ DCS

1:1 randomization

Gazelle™ BMS

Clinical Follow-up

Primary safety endpoint: **Composite of cardiac death, MI, definite/probable stent thrombosis at 1 year (non inferiority)**

Primary efficacy endpoint: **Clinically driven TLR at 1 year (Superiority)**

DAPT mandated for 1 month only, followed by long term SAPT

Inclusion Criteria (One or More)

- Age ≥ 75 years
- OAC planned after PCI
- Baseline Hb < 11g / dl or transfusion during prior 4 weeks
- Planned major surgery (within next year)
- Cancer diagnosed or treated ≤ 3 years
- Creatinine clearance < 40 ml / min
- Hospital admission for bleeding during past year
- Thrombocytopenia (< 100.000 / mm3)
- Any prior intra-cerebral bleed
- Any stroke during the past year
- Severe liver disease
- NSAID or steroids planned after PCI
- Anticipated poor DAPT compliance for other medical reason

Determination of Trial Size

Predicted event rates in BMS control arm

- Composite safety endpoint (cardiac death, MI and ST) 8%
- Efficacy endpoint (clinically-driven TLR) 10%

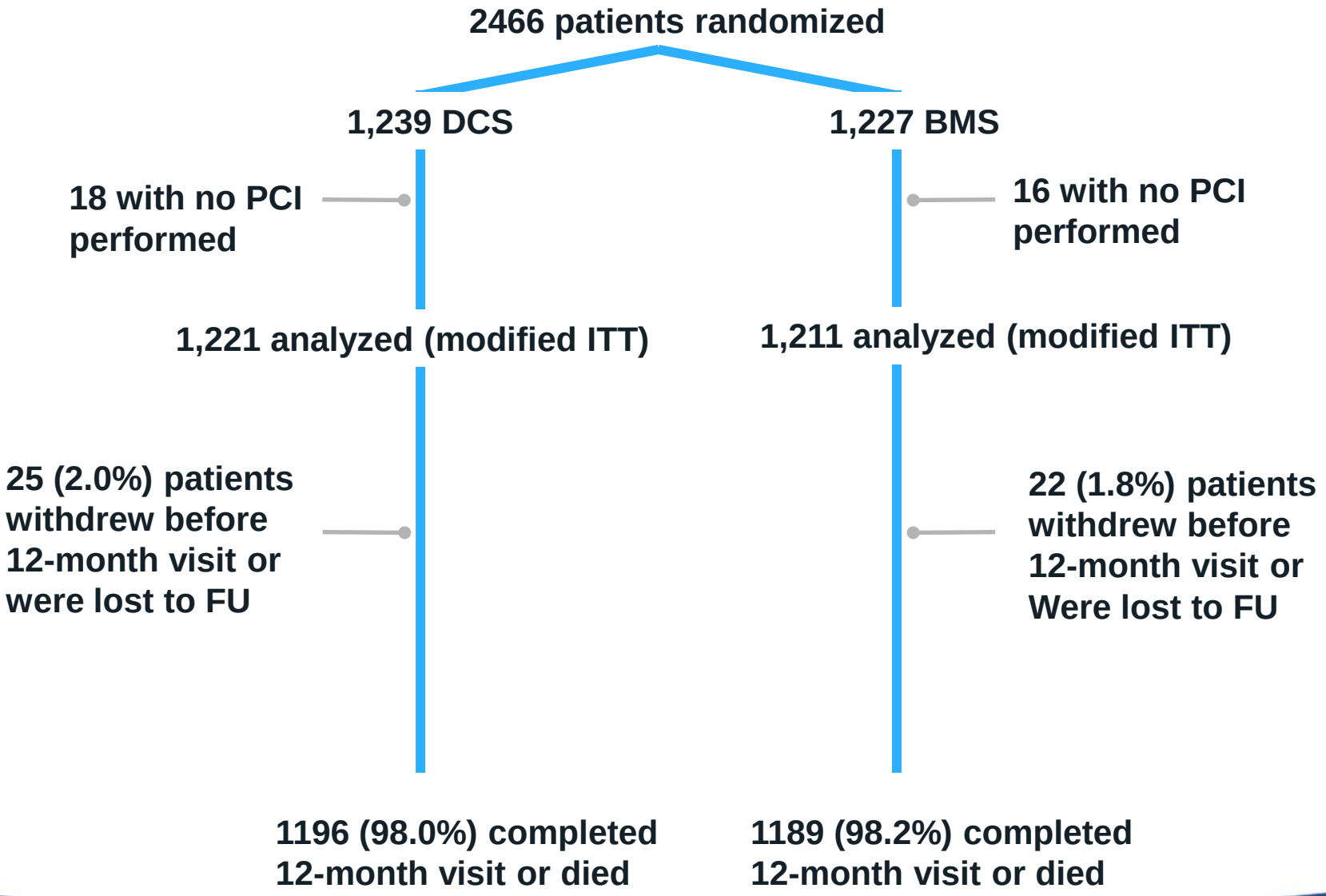
Patients per group: 1228

Endpoints

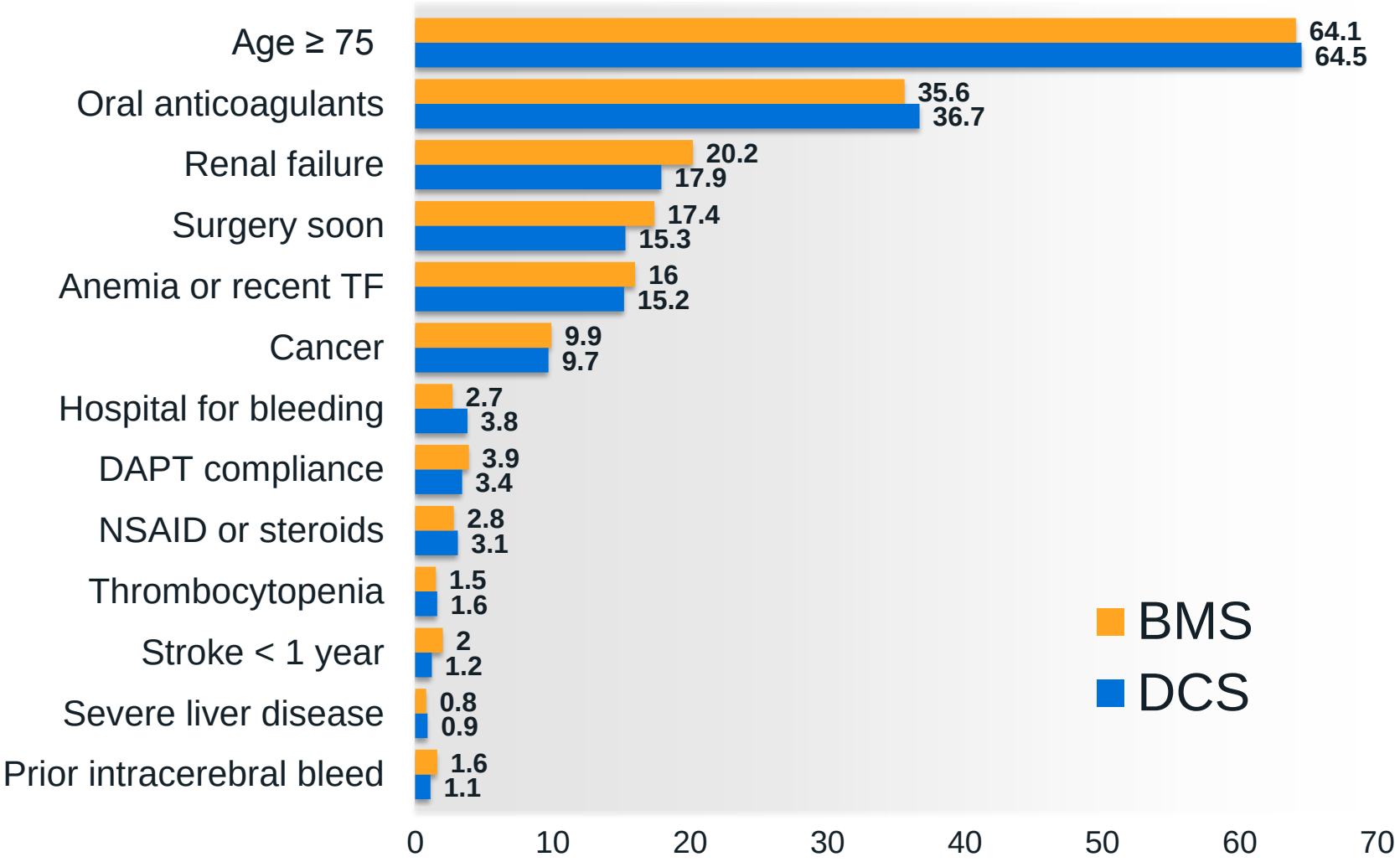
- **Safety:**
  > 80% power to demonstrate non-inferiority with margin 3.2%
- **Efficacy:**
  > 80% power to detect a 3.3% reduction in c-TLR

Both with one-sided alpha 0.025

Enrollment and Follow-Up



Inclusion Criteria Applied (1.7 criteria / patient)



Significance of LEADERS FREE Trial

- This is the first time that a PCI population characterized by an increased bleeding risk is specifically evaluated.
- Included patients are extremely different from "all-comers" in terms of their advanced age and associated major comorbidities.
- The trial is primarily designed to evaluate the efficacy and safety benefits of the BioFreedom DCS in this population, but it will also help to better define the relative thrombotic and bleeding risks that are faced by all "HBR" patients.

Baseline Characteristics

	DCS (%)	BMS (%)
Mean age	75.7 + 9.4	75.7+9.3
Female gender	29.8	30.9
BMI	27.5 ± 4.8	27.2 ± 4.6
Diabetes	34.0	32.3
NSTEMI presentation	22.4	23.2
STEMI presentation	4.7	4.0
Prior MI	19.6	21.4
Prior PCI	22.2	21.9
Prior CABG	9.4	10.1
Multivessel CAD	62.9	61.6
Congestive heart failure	14.4	12.4
Atrial fibrillation	34.9	34.6
Peripheral vascular disease	15.7	15.8
Chronic obstructive lung disease	10.9	11.7

None of the baseline characteristics differ at $p < 0.05$

Index Procedure

	DCS (%)	BMS (%)
Radial access	60.7	58.7
Staged procedure	4.5	5.9
Multi-lesion procedure	37.8	35.3
Multi-vessel procedure	21.8	21.4
Number of treated lesions / patient	1.6 ± 0.8	1.6 ± 0.9
LMS	3.0	3.9
SVG	1.4	1.8
Bifurcation	14.9	16.0
ISR	2.4	2.6
CTO	5.0	4.4

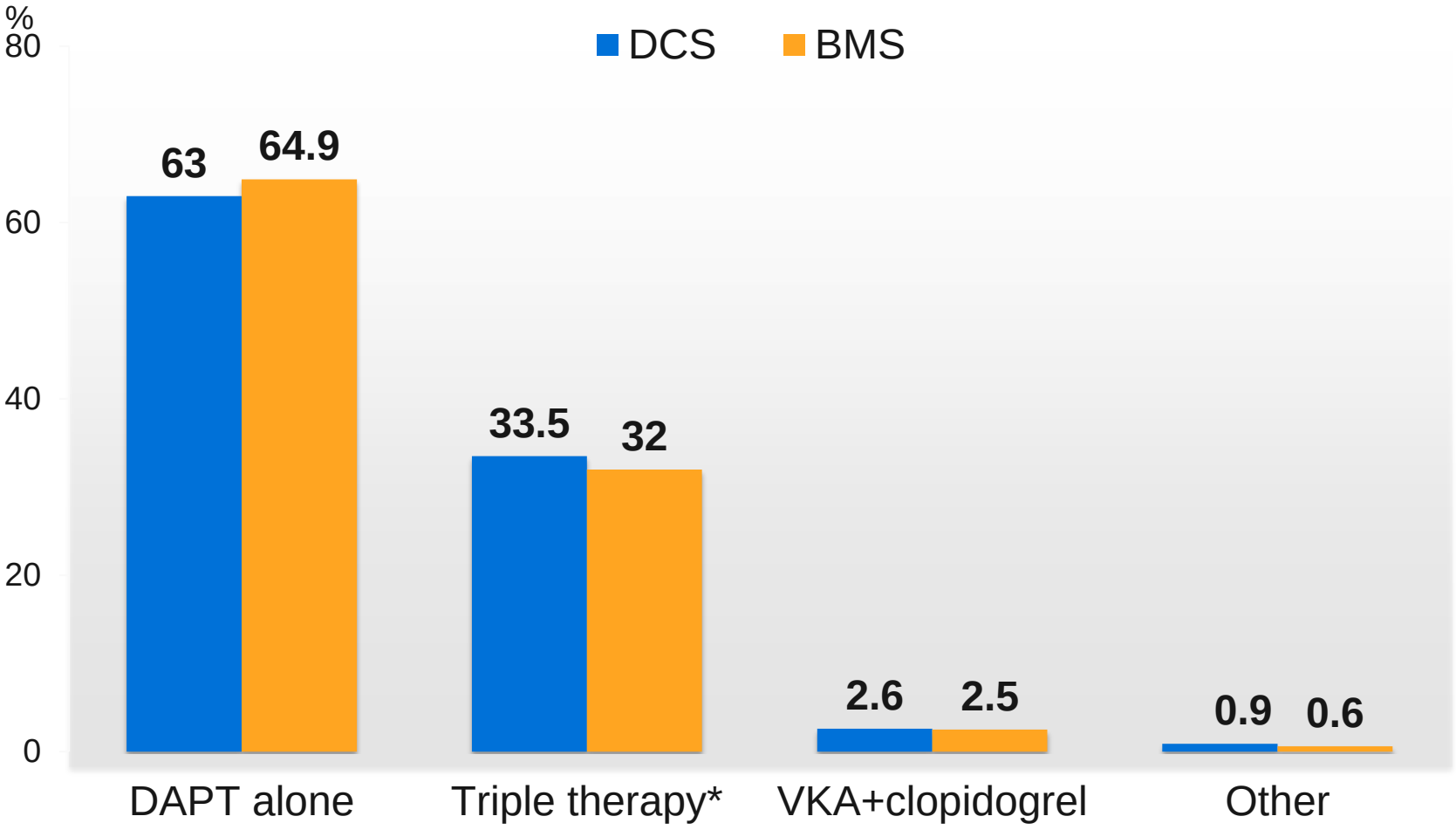
None of the procedure characteristics differ at $p < 0.05$

Index Procedure (Continued)

	DCS	BMS
Mean stent diameter	3.0 ± 0.4	3.0 ± 0.4
Mean total implanted stent length / patient	34.5 ± 23.1	33.4 ± 23.4
Mean number of stents implanted / patient	1.9 ± 1.1	1.8 ± 1.2
Lesion success	97.7	98.0
Device success	97.7	97.6
Procedure success	94.4	93.7
UFH during procedure	90.5	89.4
LMWH during procedure	8.4	8.8
Bivalirudin during procedure	1.1	1.8
2b3a blocker during procedure	2.0	1.2

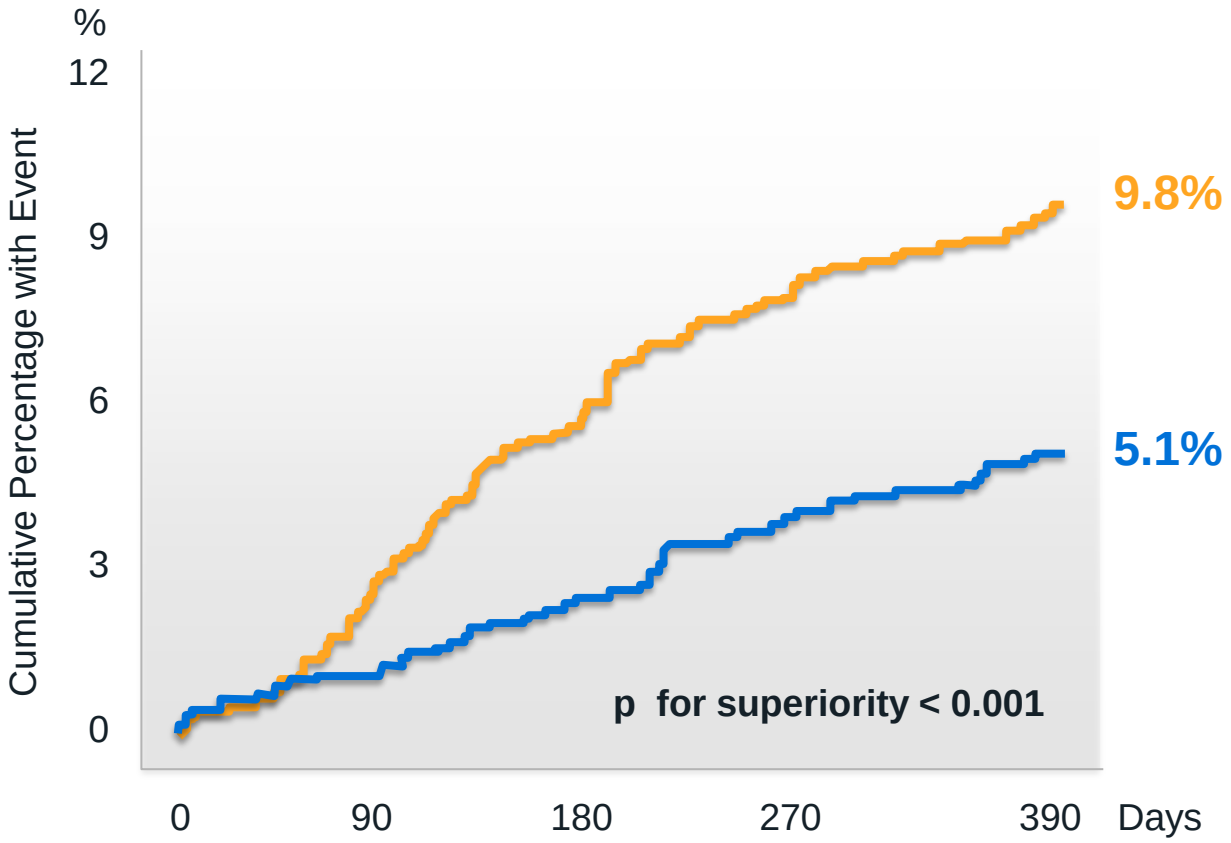
None of the procedure characteristics differ at $p < 0.05$

Antithrombotic Medication at Discharge



None of the regimens differ at p < 0.05
*** Any oral anticoagulant + DAPT**

Primary Efficacy Endpoint (Clinically-Driven TLR)



Number at Risk

DCS	1221	1167	1130	1098	1053
BMS	1211	1131	1072	1034	984

390 days chosen for assessing primary EP to capture potential evens driven by the 360 day FU contact

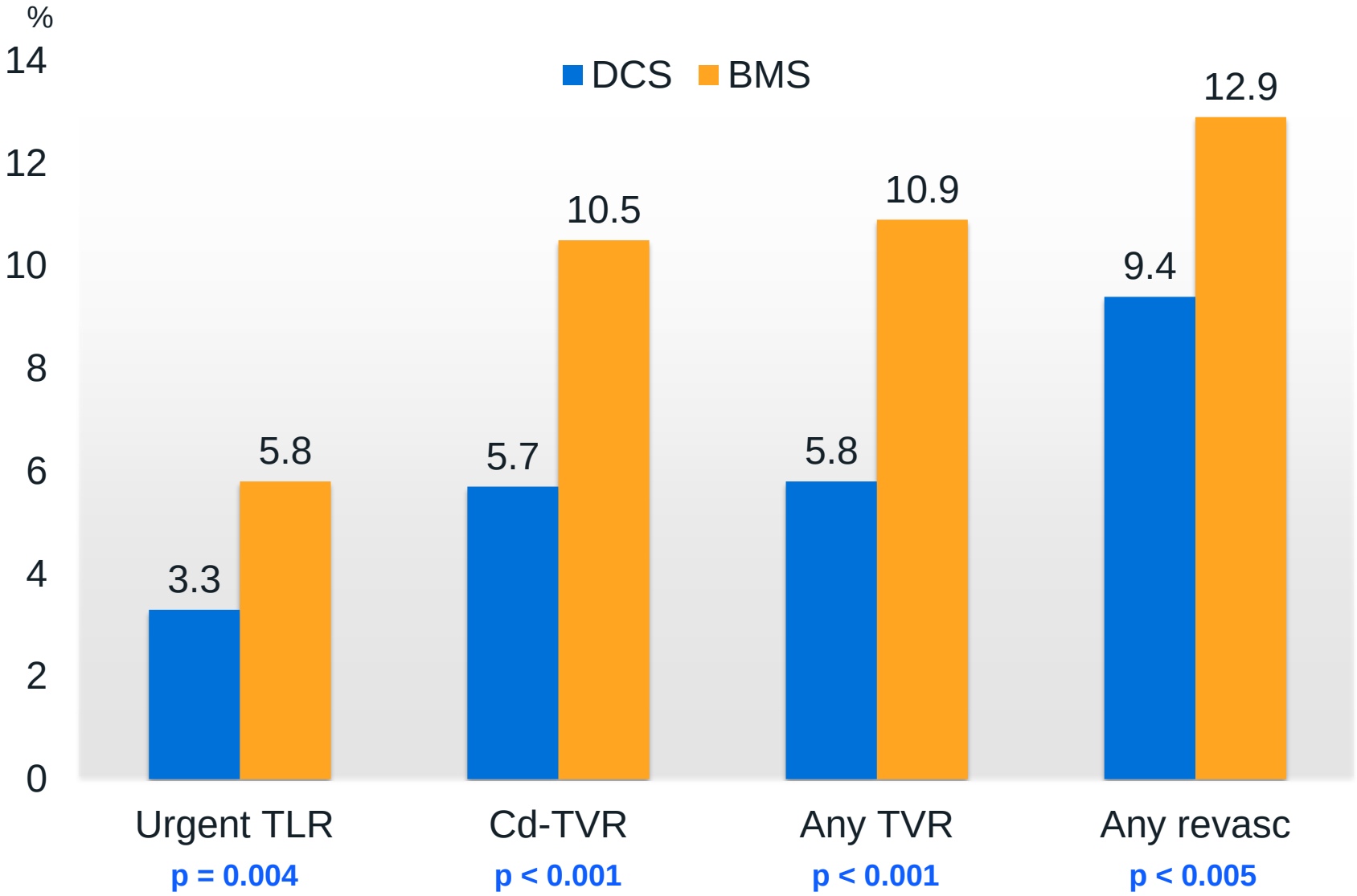
Primary Efficacy Endpoint

Primary Efficacy Endpoint	DCS (n=1221)	BMS (n=1211)
Clinically driven TLR at 390 days	**59 (5.1%)**	**113 (9.8%)**

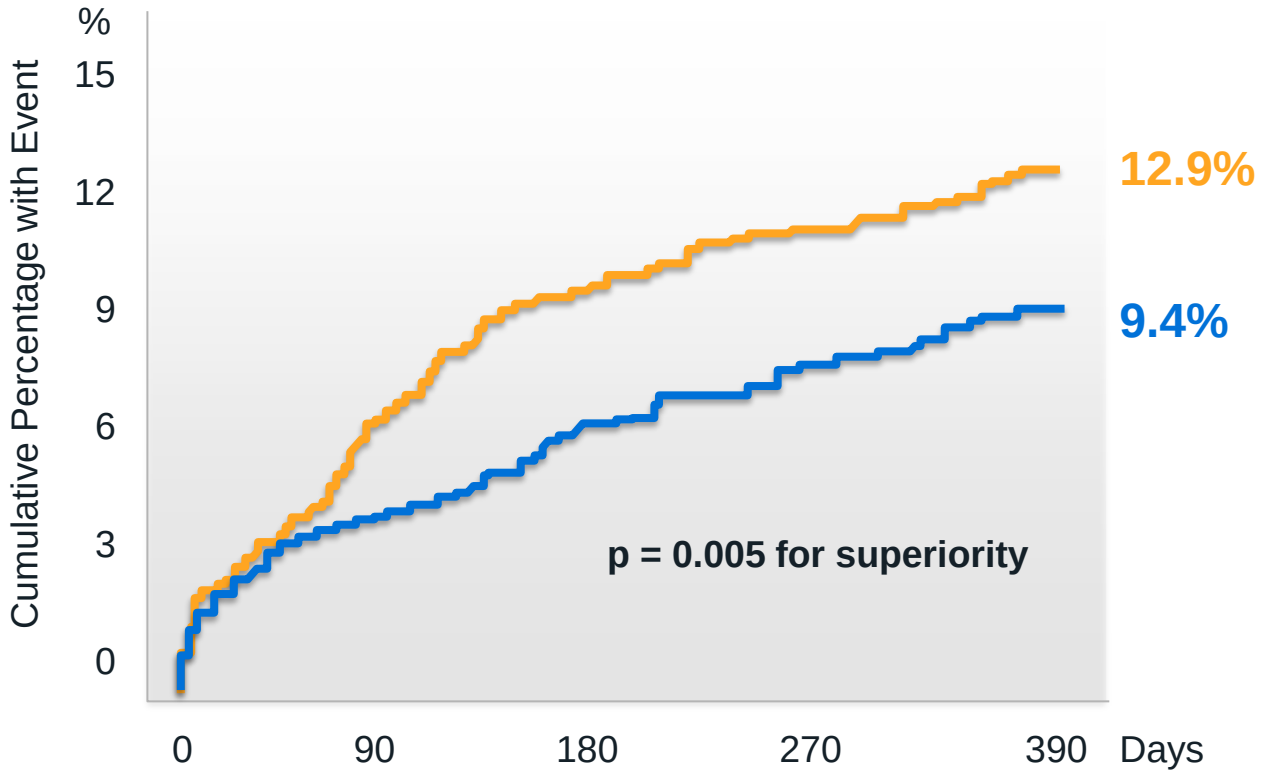
Difference:

- -4.8% (95% CI = -6.9% to -2.6%)
- HR 0.50, (95% CI = 0.37 – 0.69)
- p<0.001 for superiority

Secondary Efficacy Endpoints



Primary Safety Endpoint (Cardiac Death, MI, ST)



Number at Risk

DCS	1221	1146	1105	1081	1045
BMS	1211	1115	1066	1037	1000

390 days chosen for assessing primary EP to capture potential events driven by the 360 day FU contact

Primary Safety Endpoint

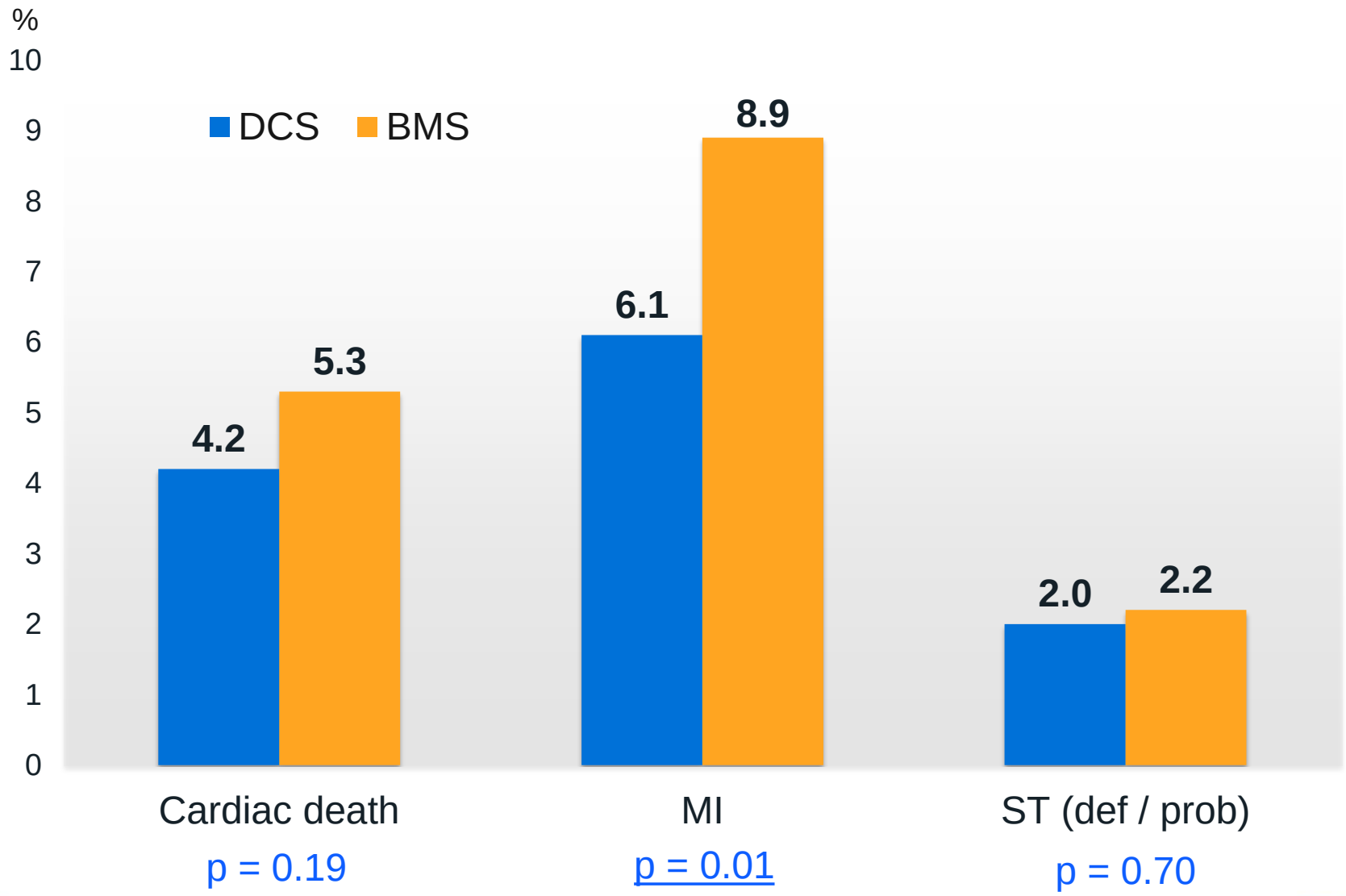
Primary Safety Endpoint*	DCS (n=1221)	BMS (n=1211)
Cardiac Death, Myocardial Infarction, or Stent Thrombosis at 390 days	**112 (9.4%)**	**154 (12.9%)**

Risk difference:

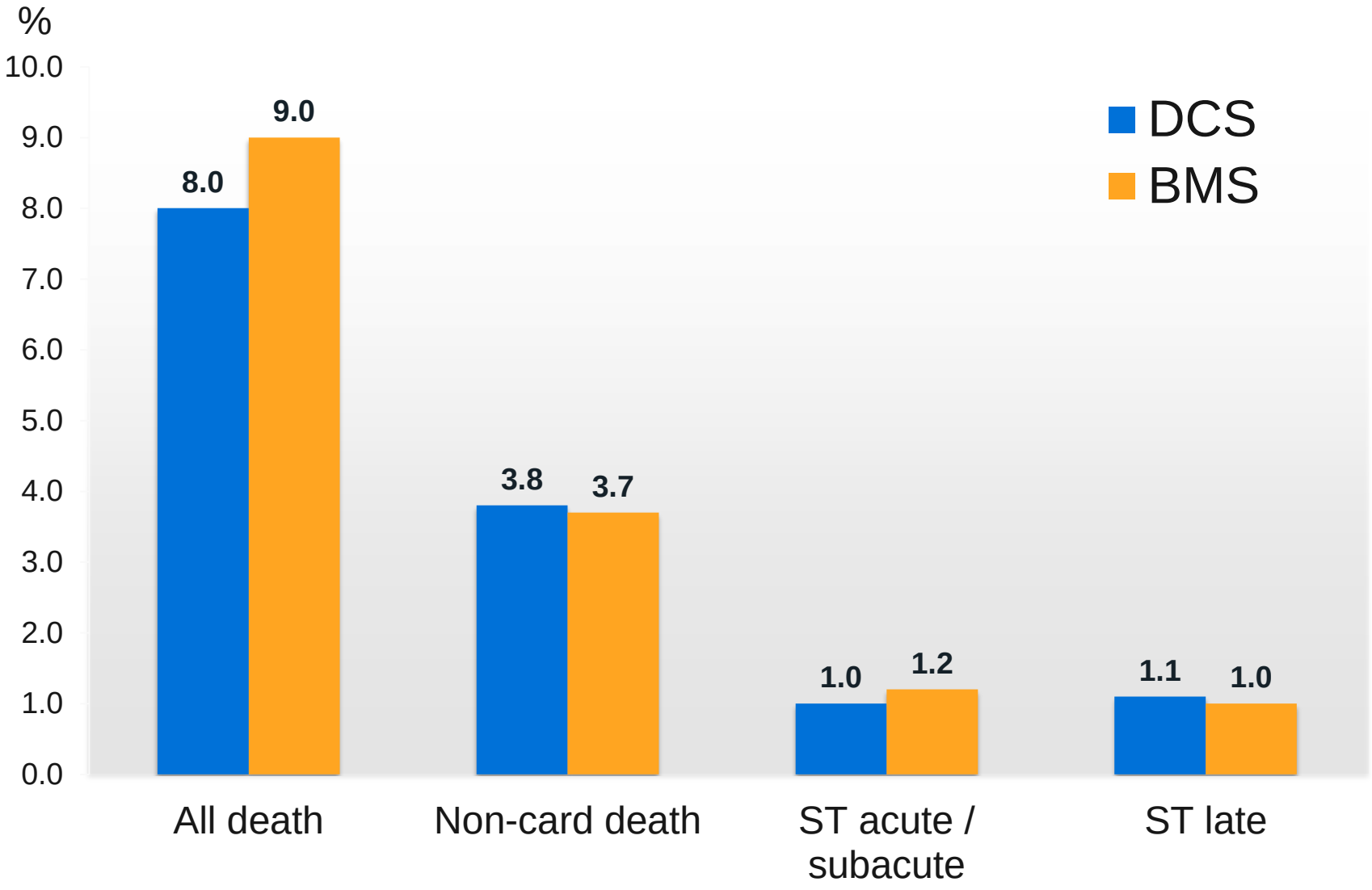
- -3.6% (95% CI -6.1% to -1.0%)
- HR 0.71, (95% CI = 0.56 – 0.91)
- p < 0.0001 for non-inferiority
- p = 0.005 for superiority

*** 3rd Universal definition of MI, Thygesen K et al Circulation 2012;126:2020 –2035**
ARC definition, Cutlip D et al. Circulation 2007; 115: 2344-51

Components of Safety Endpoint



Selected Secondary Safety Endpoints

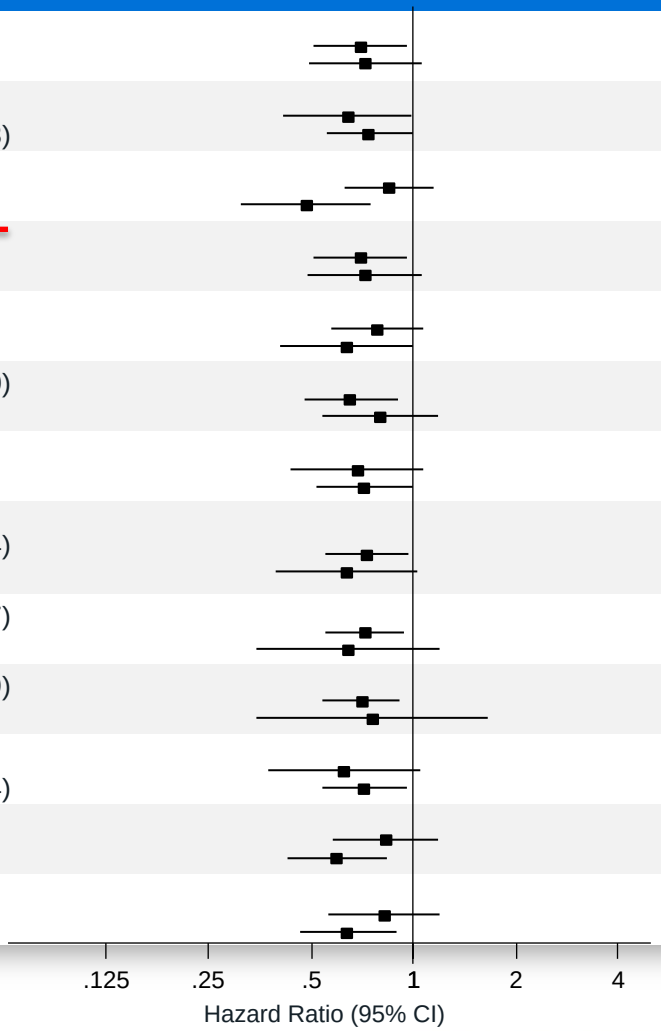


None of these endpoints differ at $p < 0.05$

Subgroups

Composite safety endpoint (cardiac death, MI, ST)

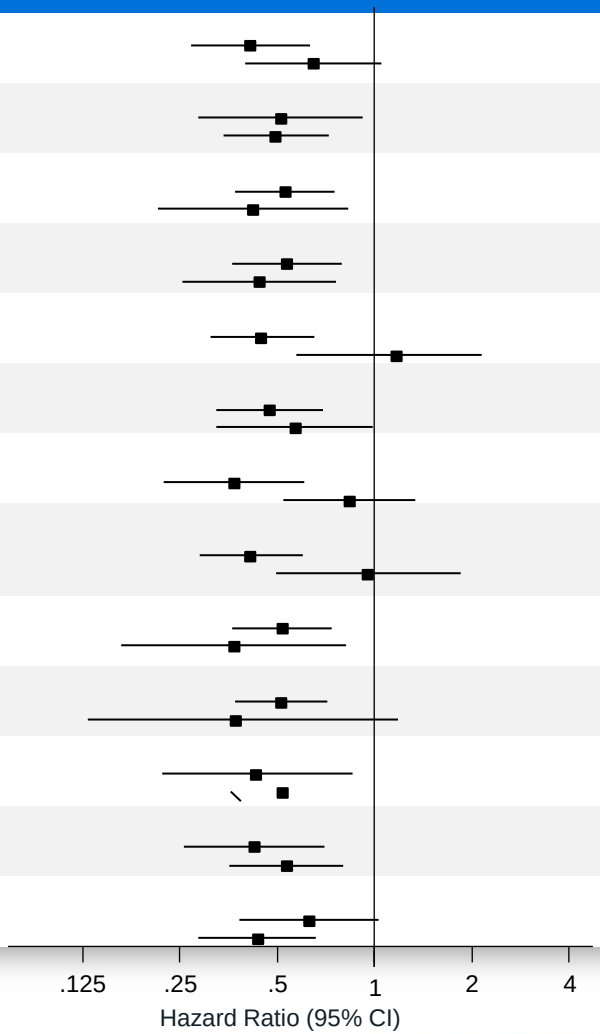
Category		DCS: Events (%)	BMS: Events (%)	P-value for interaction
Age >80	No	65 (8.3)	92 (11.6)	0.86
	Yes	47 (11.5)	62 (15.5)	
Male	No	34 (9.6)	53 (14.4)	0.59
	Yes	78 (9.3)	101 (12.3)	
ACS at admission	No	82 (9.4)	95 (10.9)	0.04
	yes	30 (9.3)	59 (18.5)	
Diabetes	No	65 (8.3)	93 (11.5)	0.90
	Yes	47 (11.5)	61 (15.9)	
Renal failure at admission	No	73 (8.3)	89 (10.4)	0.46
	Yes	31 (14.7)	53 (22.2)	
Planed OAC at randomization	No	66 (8.7)	100 (13.0)	0.44
	Yes	46 (10.5)	54 (12.8)	
Crusade score > median (35)	No	33 (6.4)	48 (9.1)	0.86
	Yes	63 (13.6)	88 (18.6)	
Anemia, transfusion or bleeding leading to hospitalization	No	84 (8.5)	113 (11.4)	0.63
	Yes	28 (13.6)	41 (20.3)	
Planned major surgery in following year	No	93 (9.4)	123 (12.7)	0.74
	yes	16 (8.4)	27 (12.9)	
Cancer in last 3 years*	No	101 (9.3)	139 (12.9)	0.87
	yes	11 (9.6)	15 (12.9)	
Multi-vessel disease at admission	No	24 (5.4)	39 (8.6)	0.64
	yes	84 (11.4)	112 (15.4)	
Total stent length > 30 mm	No	54 (8.0)	68 (9.6)	0.19
	Yes	56 (10.9)	82 (17.4)	
Minimal stent diameter < 3 mm	No	49 (8.3)	59 (10.1)	0.33
	Yes	61 (10.2)	91 (15.3)	



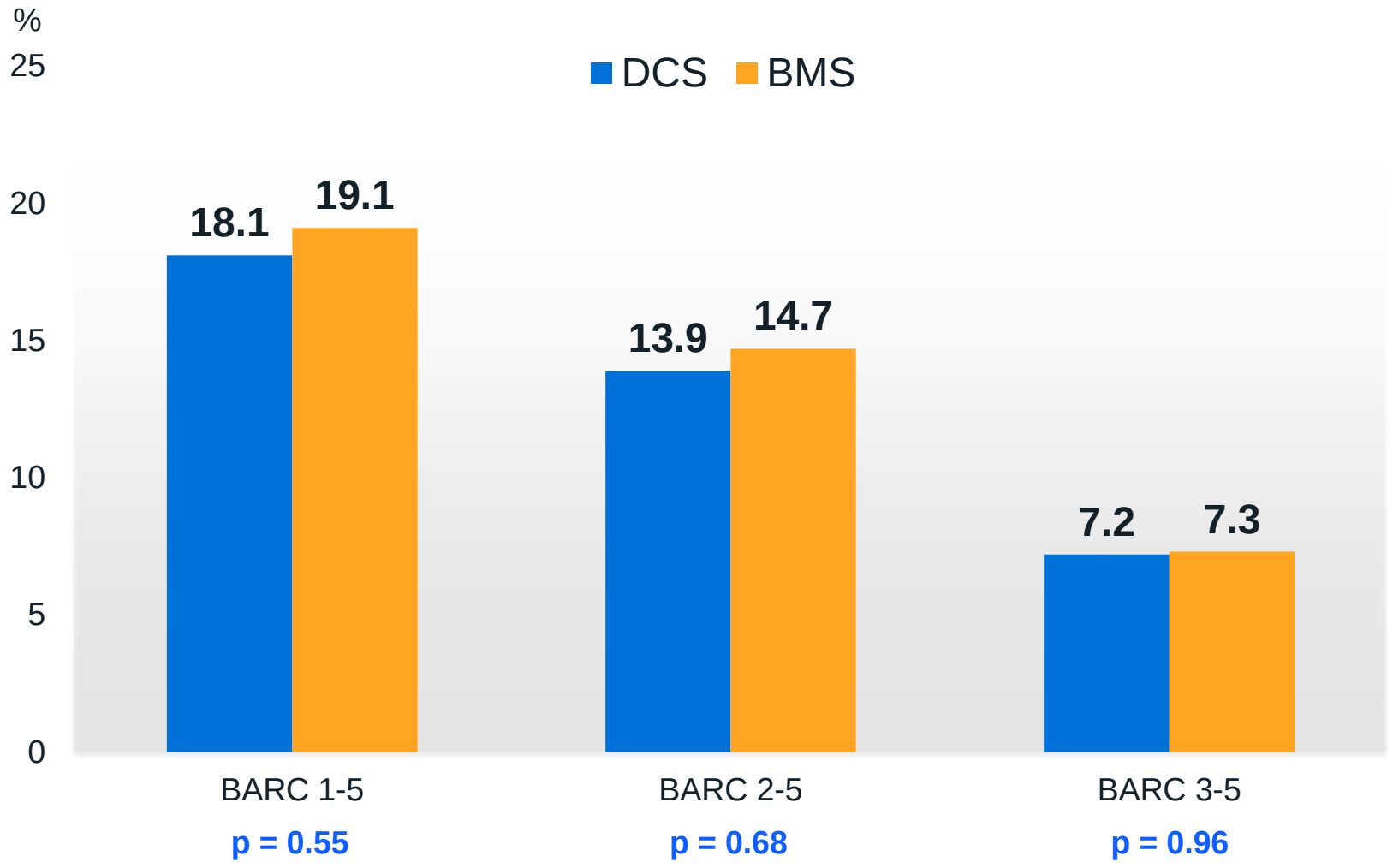
Subgroups (continued)

Efficacy endpoint (clinically driven TLR)

Category		N	DCS: Events (%)	BMS: Events (%)	P-value for interaction
Age >80	No	1602	31 (4.0)	72 (9.4)	0.17
	Yes	830	28 (7.1)	41 (10.6)	
Male	No	738	17 (5.0)	33 (9.3)	0.92
	Yes	1694	42 (5.1)	80 (10.0)	
ACS at admission	No	1773	47 (5.5)	86 (10.1)	0.55
	yes	659	12 (3.9)	27 (9.0)	
Diabetes	No	1622	40 (5.3)	74 (9.4)	0.57
	Yes	805	19 (4.7)	39 (10.7)	
Renal failure at admission	No	1754	42 (4.9)	88 (10.6)	0.02
	Yes	466	16 (7.9)	15 (6.7)	
Planed OAC at randomization	No	1553	39 (5.3)	80 (10.7)	0.61
	Yes	879	20 (4.7)	33 (8.2)	
Crusade score > median (35)	No	1061	21 (4.1)	56 (10.7)	0.02
	Yes	962	33 (7.5)	39 (8.7)	
Anemia, transfusion or bleeding leading to hospitalization	No	2007	41 (4.2)	95 (9.9)	0.03
	Yes	425	18 (9.2)	18 (9.6)	
Planned major surgery in following year	No	2002	49 (5.1)	89 (9.5)	0.43
	yes	404	8 (4.3)	23 (11.5)	
Cancer in last 3 years*	No	2193	55 (5.2)	102 (9.8)	0.59
	yes	239	4 (3.5)	11 (9.8)	
Multi-vessel disease at admission	No	906	12 (2.8)	28 (6.4)	0.64
	yes	1493	46 (6.5)	84 (12.0)	
Total stent length > 30 mm	No	1409	21 (3.2)	51 (7.4)	0.48
	Yes	999	38 (7.6)	61 (13.6)	
Minimal stent diameter < 3 mm	No	1195	26 (4.5)	41 (7.2)	0.26
	Yes	1213	33 (5.7)	71 (12.4)	



Bleeding During 12 Months Follow-Up



Conclusions

- ✓ LEADERS FREE is the first randomized clinical trial dedicated to HBR patients
- ✓ Such patients are often excluded from stent and drug trials, constitute a rapidly growing proportion of PCI candidates and suffer high event rates
- ✓ Together with a one-month only DAPT course, the use of a BA9-DCS was both significantly safer and more effective than a control BMS in HBR patients

Thank You For Your Attention!

Procedural Data

All patients – 1st and 2nd Cohorts (N=182)

Variable	BFD SD N = 60	BFD LD N = 62	TAXUS N = 60
Stents per Patient (mean ± SD)	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.2
Predilatation (%)	88	92	92
Postdilatation (%)	18	23	22
Final TIMI 3 Flow (%)	100	100	100
Device Success (%)	97	100	100
Lesion Success (%)	100	100	100
Procedural Success (%)	100	98 (1 non-Q MI)	100

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Pre-procedural QCA Analysis

All Lesions – 1st and 2nd Cohorts (N=182)

Variable	BFD SD N = 59	BFD LD N = 63	TAXUS N = 60
Lesion Length (mm)	10.6 [9.3, 13.9]	11.3 [9.8, 13.6]	11.2 [9.5, 14.0]
RVD (mm)	2.8 [2.5, 3.0]	2.8 [2.5, 3.0]	2.8 [2.5, 3.0]
MLD (mm)	0.6 [0.3, 0.9]	0.6 [0.4, 0.9]	0.7 [0.5, 0.9]
% DS	76.0 [64.3, 87.6]	77.2 [67.0, 85.8]	75.9 [67.2, 83.6]

Final QCA Analysis

All Lesions – 1st and 2nd Cohorts (N=182)

Variable	BFD SD N = 59	BFD LD N = 63	TAXUS N = 60
Acute Gain (mm)			
In-segment	1.6 [1.3, 2.0]	1.6 [1.4, 1.8]	1.6 [1.3, 2.0]
In-stent	2.0 [1.6, 2.2]	1.9 [1.7, 2.2]	1.9 [1.7, 2.2]
MLD (mm)			
In-segment	2.3 [2.0, 2.5]	2.2 [2.1, 2.5]	2.2 [2.0, 2.6]
In-stent	2.7 [2.3, 2.8]	2.6 [2.3, 2.8]	2.6 [2.4, 2.8]
% Diameter Stenosis			
In-segment	17.2 [9.4, 24.3]	16.9 [12.0, 23.0]	19.1 [12.0, 24.0]
In-stent	6.2 [3.9, 11.5]	7.4 [4.5, 9.9]	6.1 [3.6, 9.4]

BioFreedom™ Clinical trial Overview

BIOFREEDOM FIM	182	GERMANY	1:1:1 Randomized trial testing doses of BA9™ vs. TAXUS® Liberté®	In-stent late lumen loss at 12 months	Study completed 5-year follow-up	Minimum 6 months
LEADERS FREE	2466	EUROPE + CANADA AUSTRALIA + ASIA	1:1 Randomized multicenter vs. Gazelle™ BMS	1. Composite safety (cardiac death, MI, def/prob ST) 2. ci-TLR at 12 months	Enrolment completed	1 month
LEADERS FREE JAPAN	140	JAPAN	Single arm trial	1. Composite safety endpoint (cardiac death, MI, def/prob ST) 2. ci-TLR at 12 months	Enrolment completed	1 month
BIOFREEDOM USA	100	USA	Single arm trial	MACE, ST & in-stent late lumen loss at 9 months	Enrolment completed	3 months
EGO BIOFREEDOM	100	HONG KONG	Single center registry	Endothelialization from 1 to 9 months, assessed by OCT	Enrolment completed	