LEADERS FREE Trial – Two Year Outcomes

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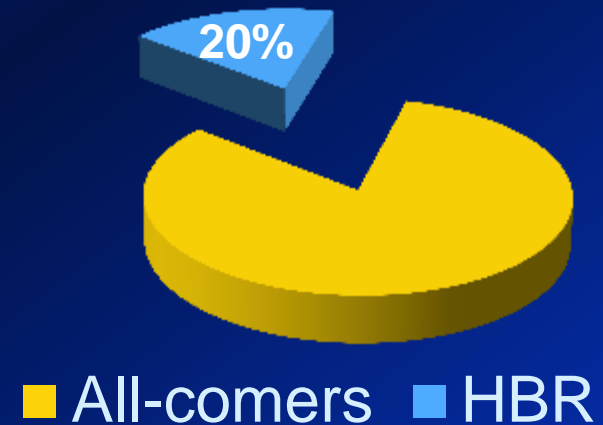
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Who are "high bleeding risk" (HBR) patients ?

- Conservative estimate – 20% of all patients
- Often excluded from trials
- Were never really studied

20%

■ All-comers ■ HBR

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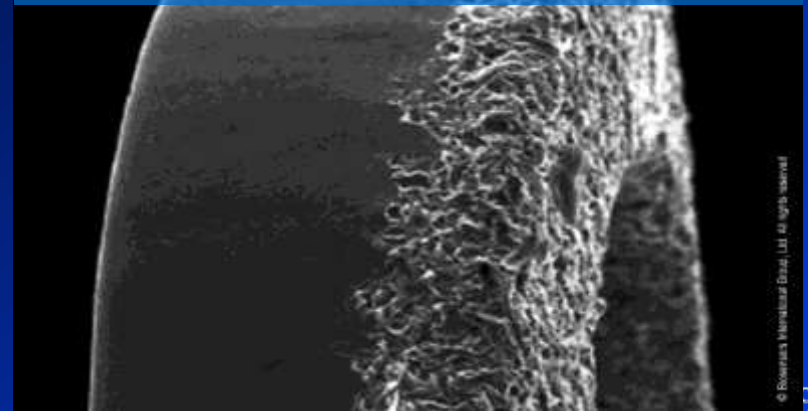HOSPITAL

Biofreedom Drug Coated Stent (DCS)

- Stent coated with biolimus A9

- Only on abluminal surface

- No polymer

- Highly lipophilic

- 98% drug transferred to vessel wall in one month

BA9™ Drug 10 Times More Lipophilic than Sirolimus[1]
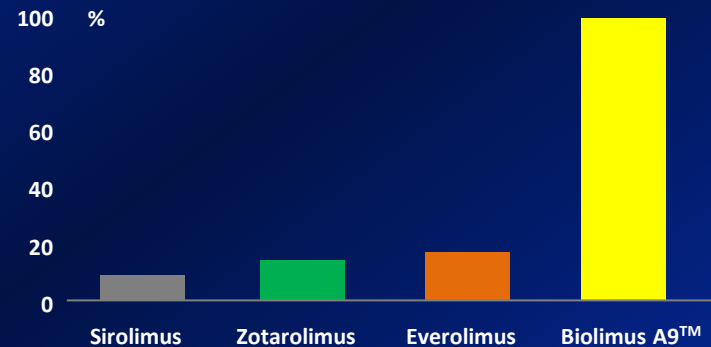
+/- 2.8% (valid for all drugs test)

Selectively Micro-Structured Surface Holds Drug in Abluminal Surface Structures

LEADERS FREE trial

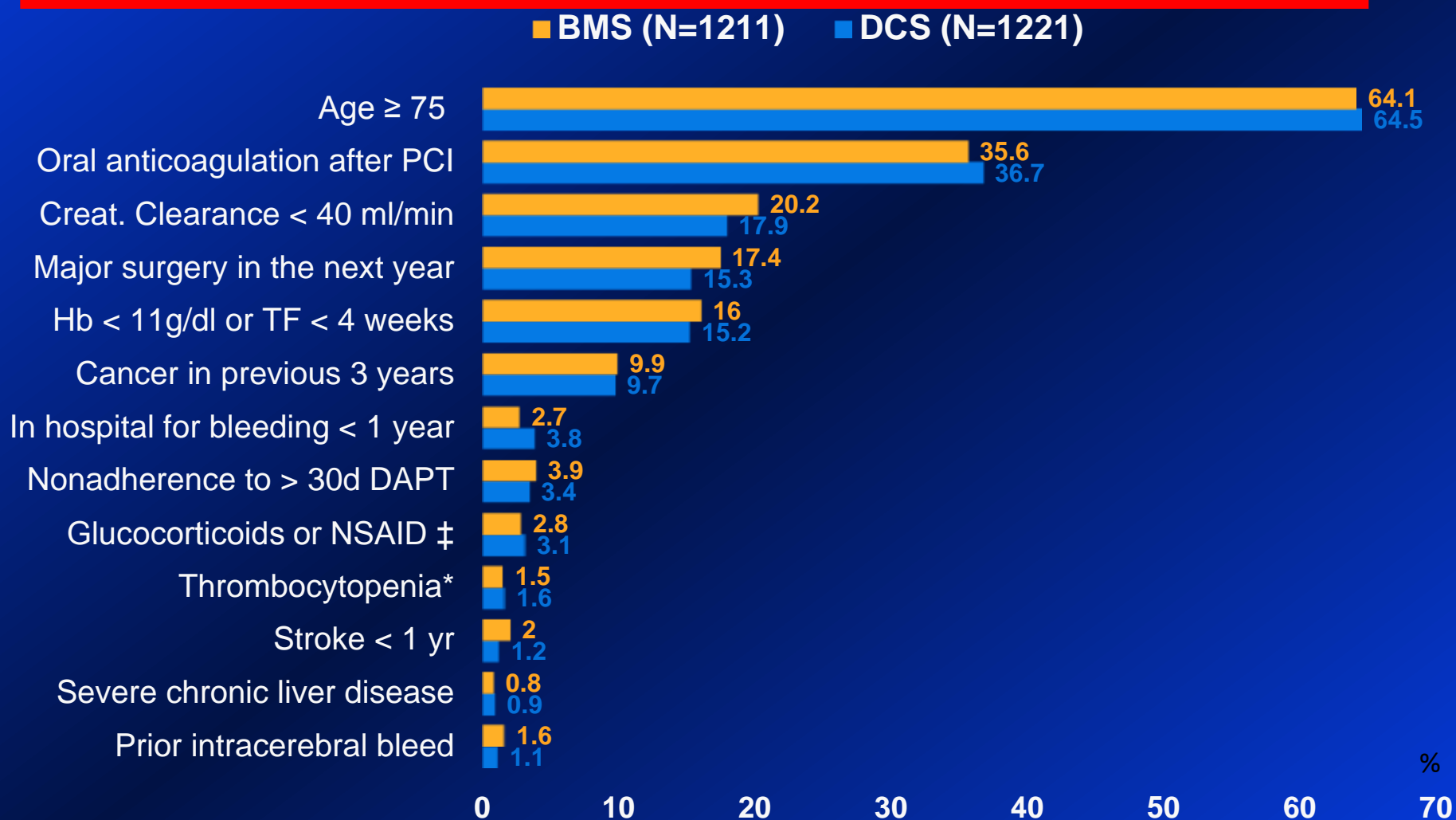- Prospective, double blind, randomized trial 2466 HBR PCI patients

BioFreedom™ DCS	**vs.**	Gazelle™ BMS

- DAPT mandated for 1 month only
- Primary safety end point – composite of death, MI, definite or probable stent thrombosis at 1 year (non-inferiority)
- Primary efficacy end point – clinically driven TLR (superiority)

Inclusion Criteria

Legend: ■ BMS (N=1211) ■ DCS (N=1221)

Criterion	BMS	DCS
Age ≥ 75	64.1	64.5
Oral anticoagulation after PCI	35.6	36.7
Creat. Clearance < 40 ml/min	20.2	17.9
Major surgery in the next year	17.4	15.3
Hb < 11g/dl or TF < 4 weeks	16	15.2
Cancer in previous 3 years	9.9	9.7
In hospital for bleeding < 1 year	2.7	3.8
Nonadherence to > 30d DAPT	3.9	3.4
Glucocorticoids or NSAID ‡	2.8	3.1
Thrombocytopenia*	1.5	1.6
Stroke < 1 yr	2	1.2
Severe chronic liver disease	0.8	0.9
Prior intracerebral bleed	1.6	1.1

%

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Baseline characteristics (similar)

	DCS (%)	BMS (%)
Age (mean ± SD)	75.7 ± 9.4	75.7 ± 9.3
Female	29.8	30.9
BMI	27.5 ± 4.8	27.2 ± 4.6
Diabetes	34.0	32.3
UA/NSTEMI/STEMI	14.5 / 22.4 / 4.7	15.9 / 23.2 / 4.0
Stable CAD	58.5	56.9
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
Prior Stroke	10.9	9.1
Peripheral vascular disease	15.7	15.8
Chronic obstructive lung disease	10.9	11.7

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Procedural details

	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
LAD	52.2	51.7
LCX	29.0	28.8
LMS	3.0	3.9
RCA	37.3	35.0
SVG	1.4	1.8
Bifurcation	14.9	16.0
ISR	2.4	2.6
CTO	5.0	4.4

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Efficacy end point

Efficacy (cd-TLR)

| DCS | BMS |
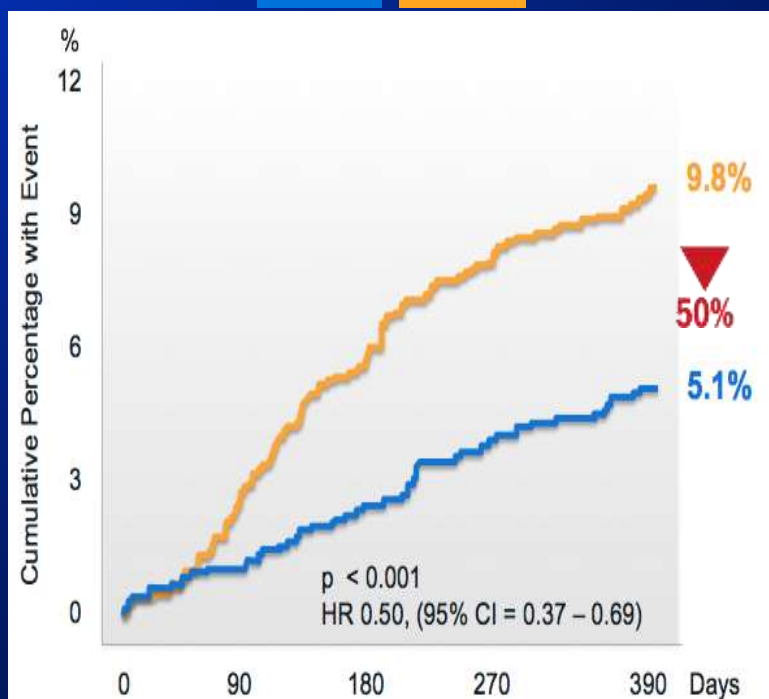
Safety (cardiac death, MI, ST)

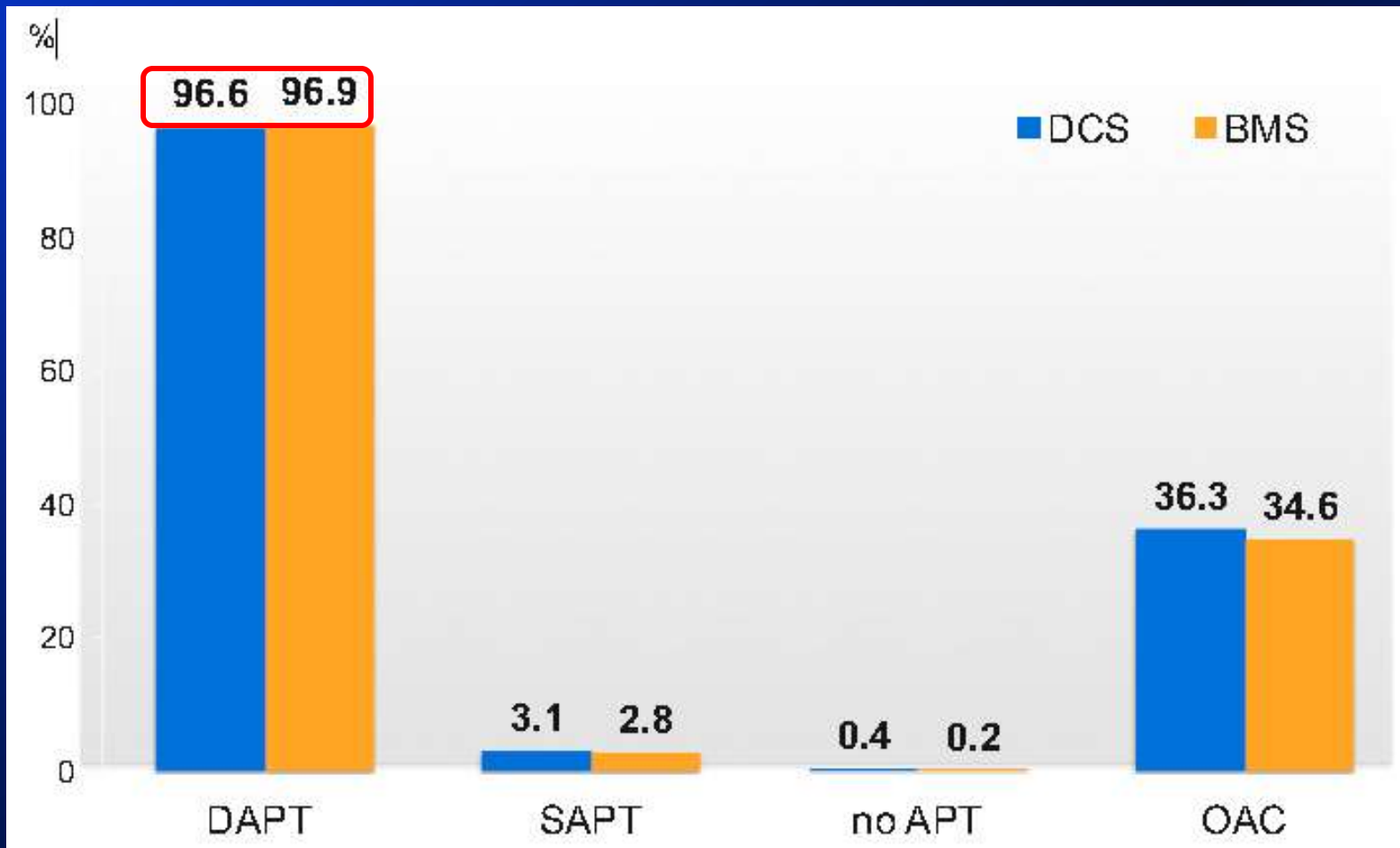| DCS | BMS |
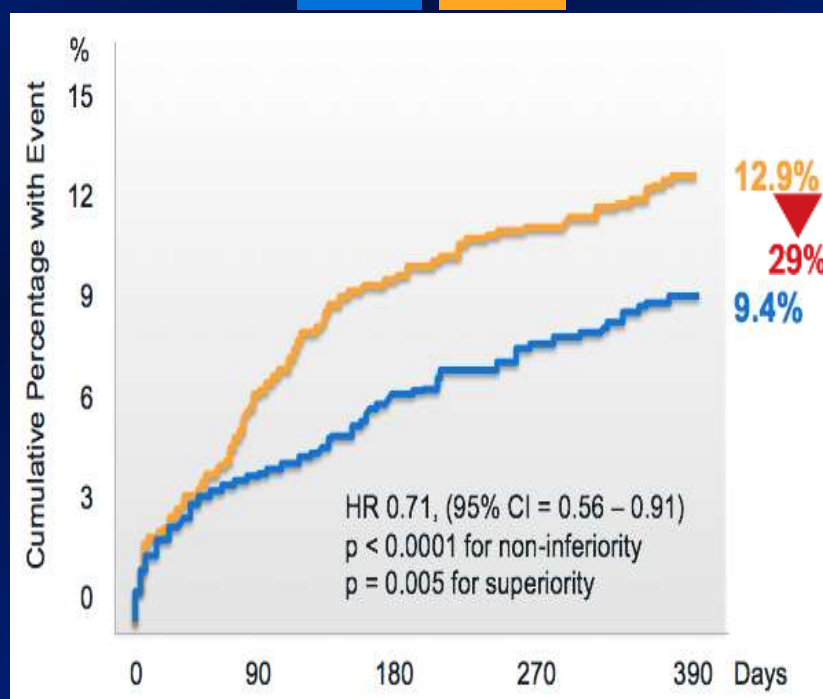
Urban P et al. N Engl J Med 2015;373:2038-47

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Two year follow-up

Two year follow-up

2466 patients randomized

1,239 DCS

1,227 BMS

18 with no PCI performed

16 with no PCI performed

1,221 analyzed (modified ITT)

1,211 analyzed (modified ITT)

28 (2.3%) patients withdrew before 24-month visit or were lost to FU

20 (1.7%) patients withdrew before 24-month visit or Were lost to FU

1193 (97.7%) completed 24-month visit or died

1191 (98.3%) completed 24-month visit or died
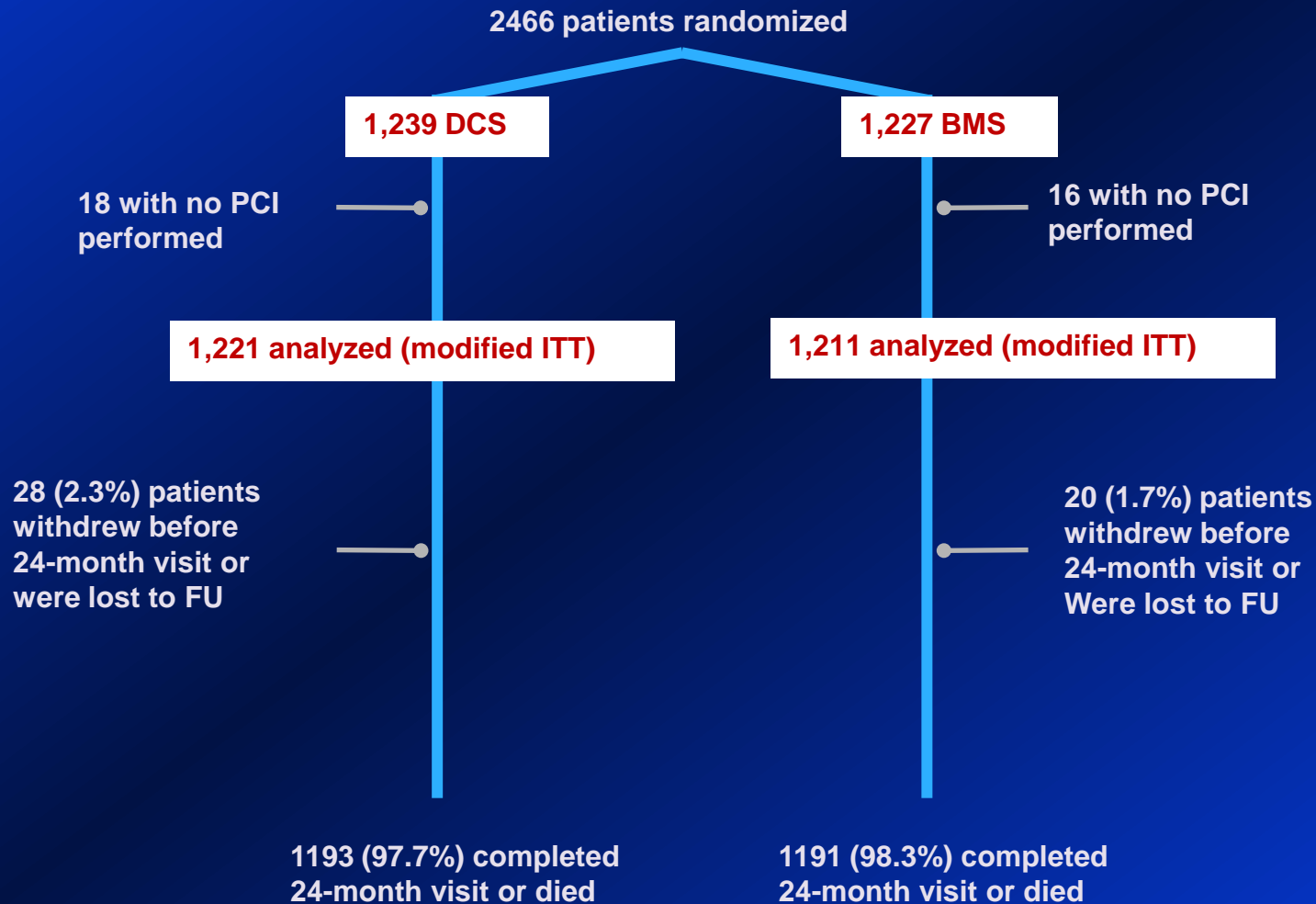
Antithrombotic drugs on discharge
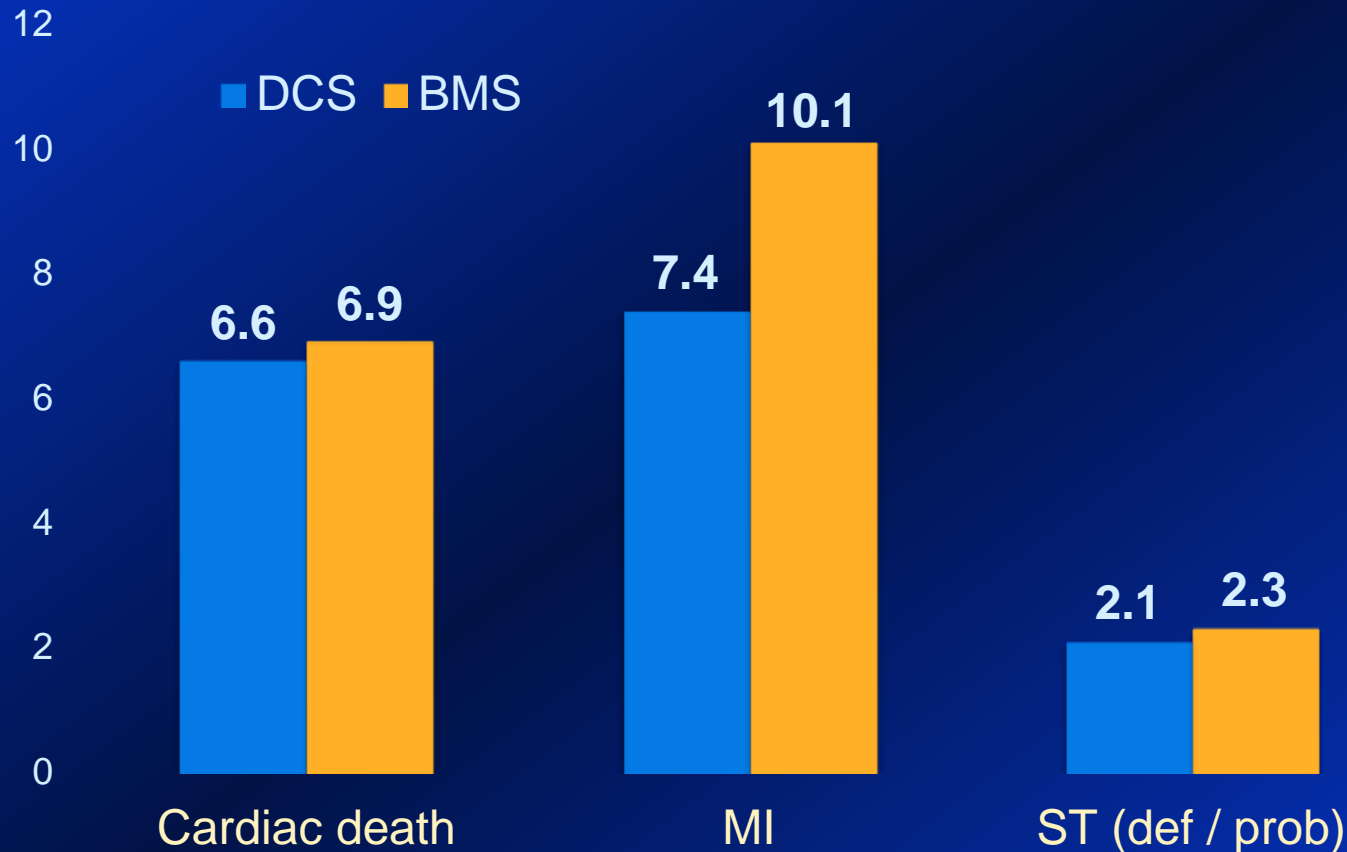
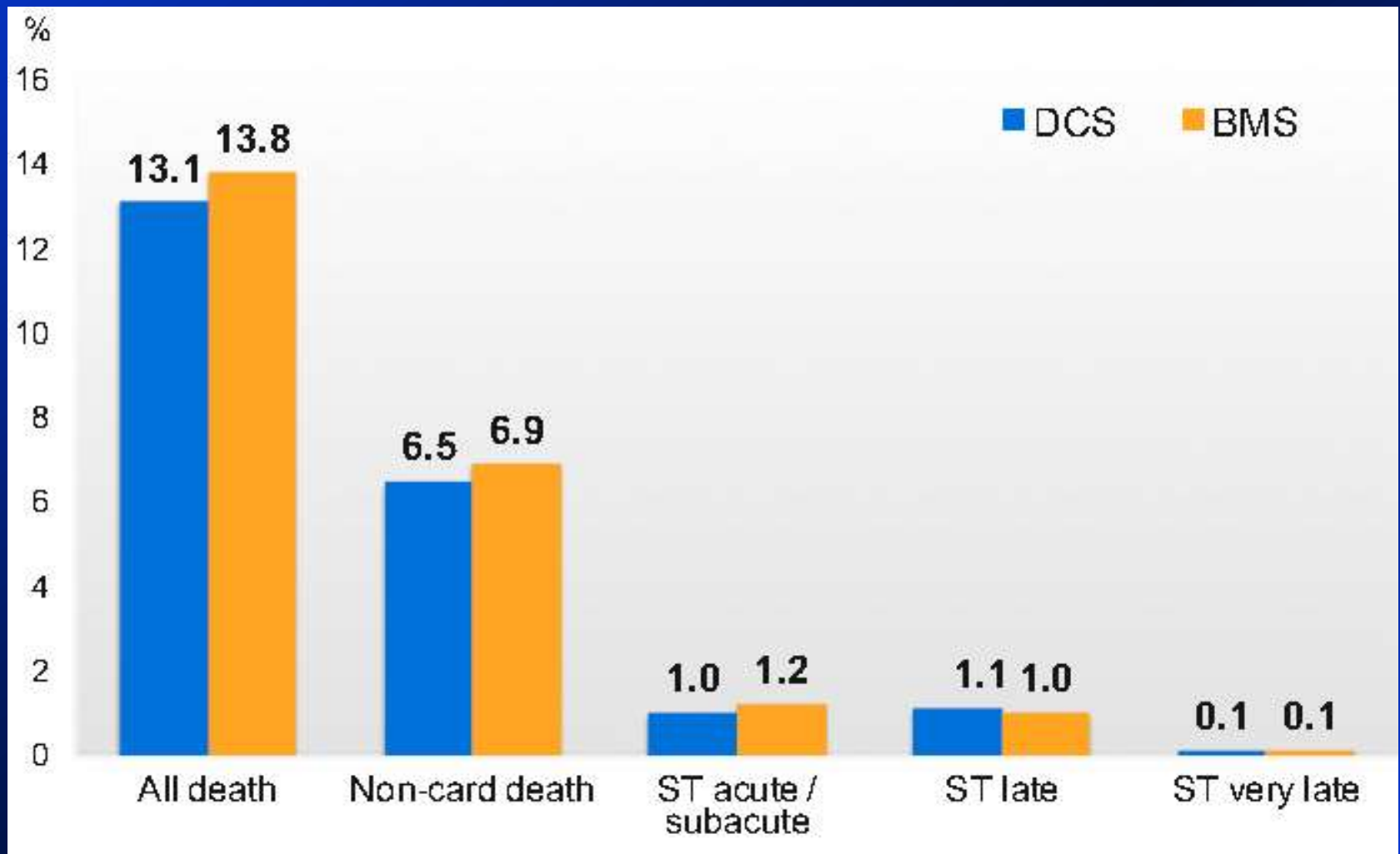

None of the regimens differ at p < 0.05

Antithrombotic drugs at two years
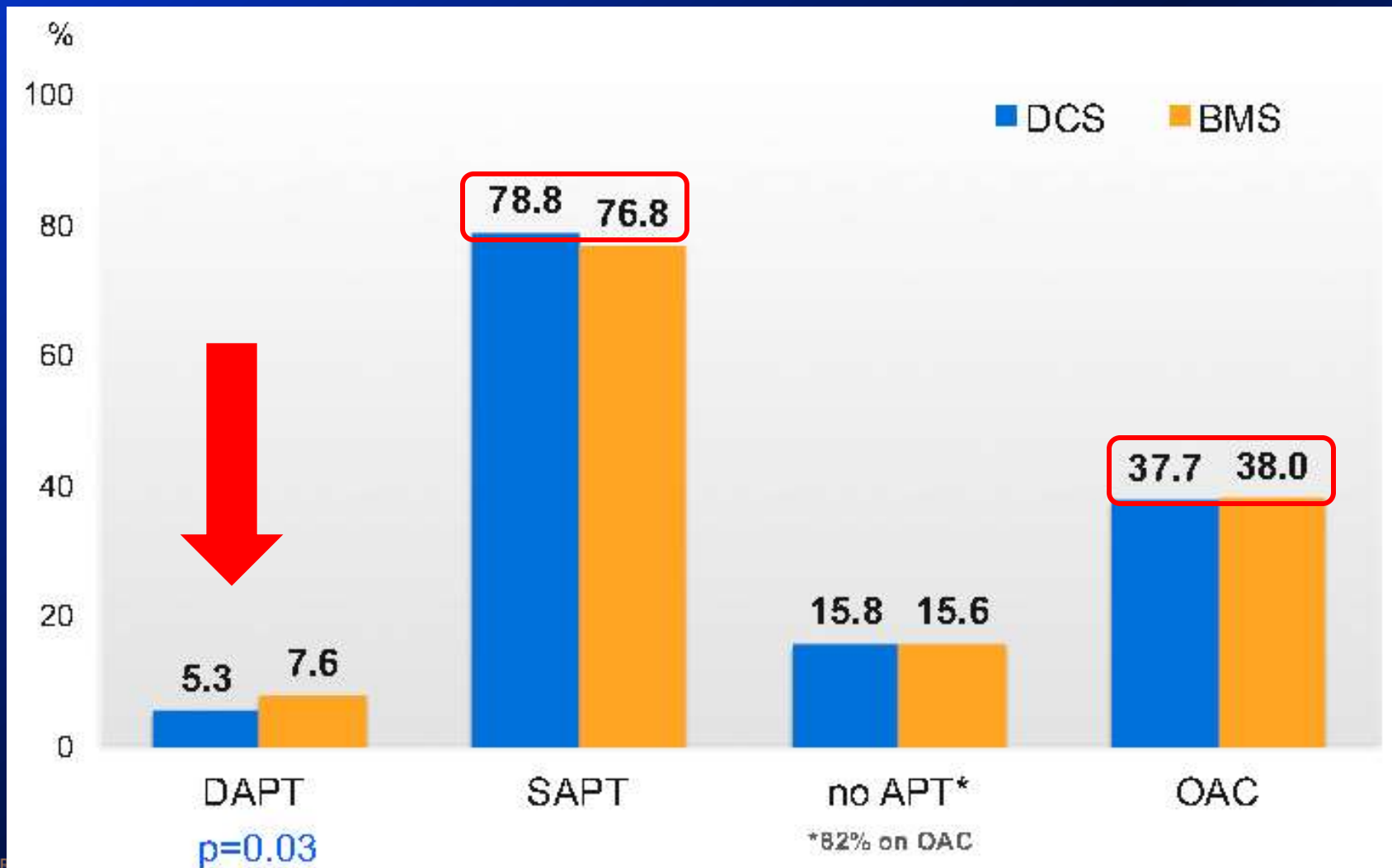
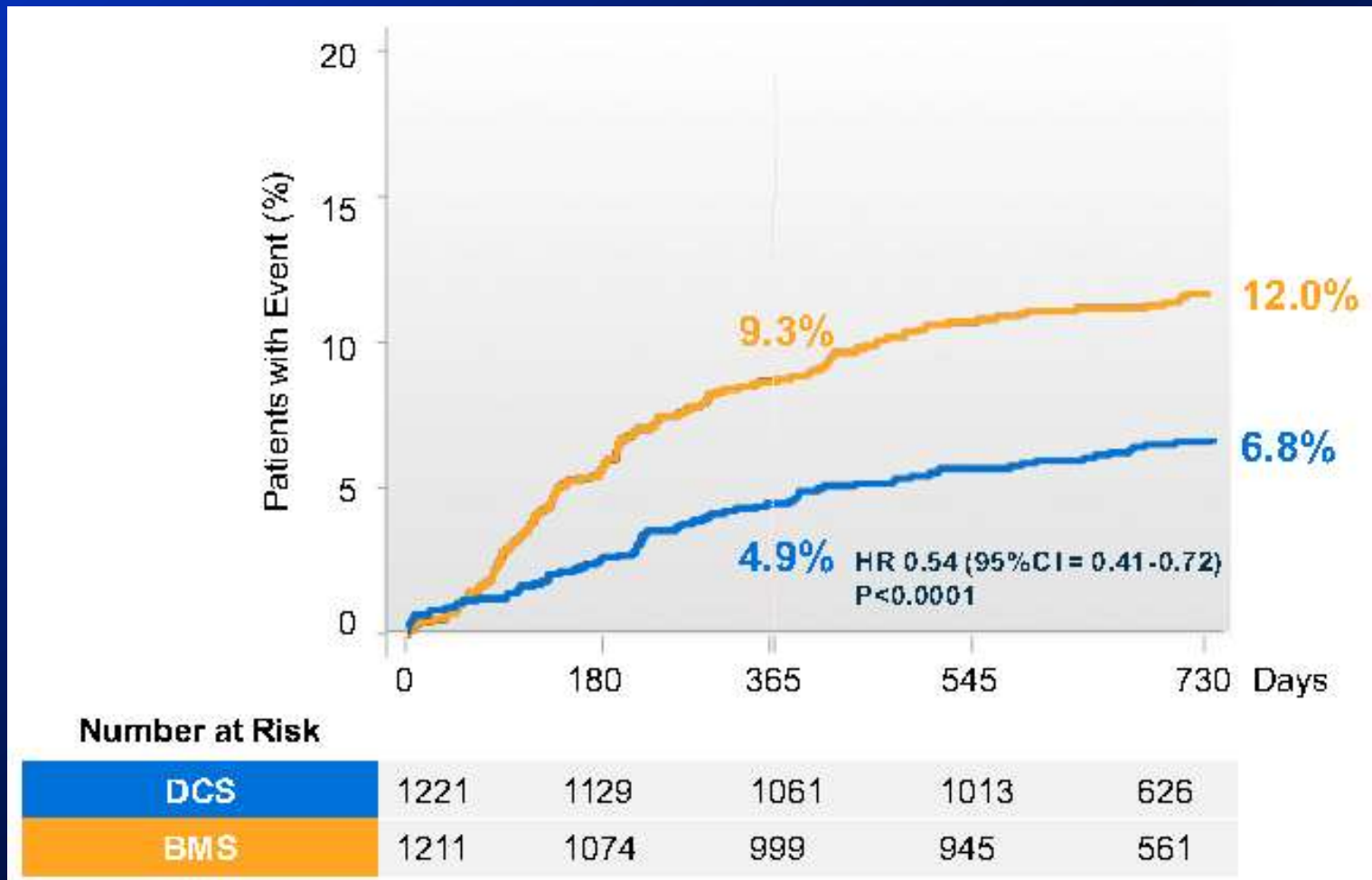# *Primary safety end point (cardiac death, MI, stent thrombosis) at 2 yrs*
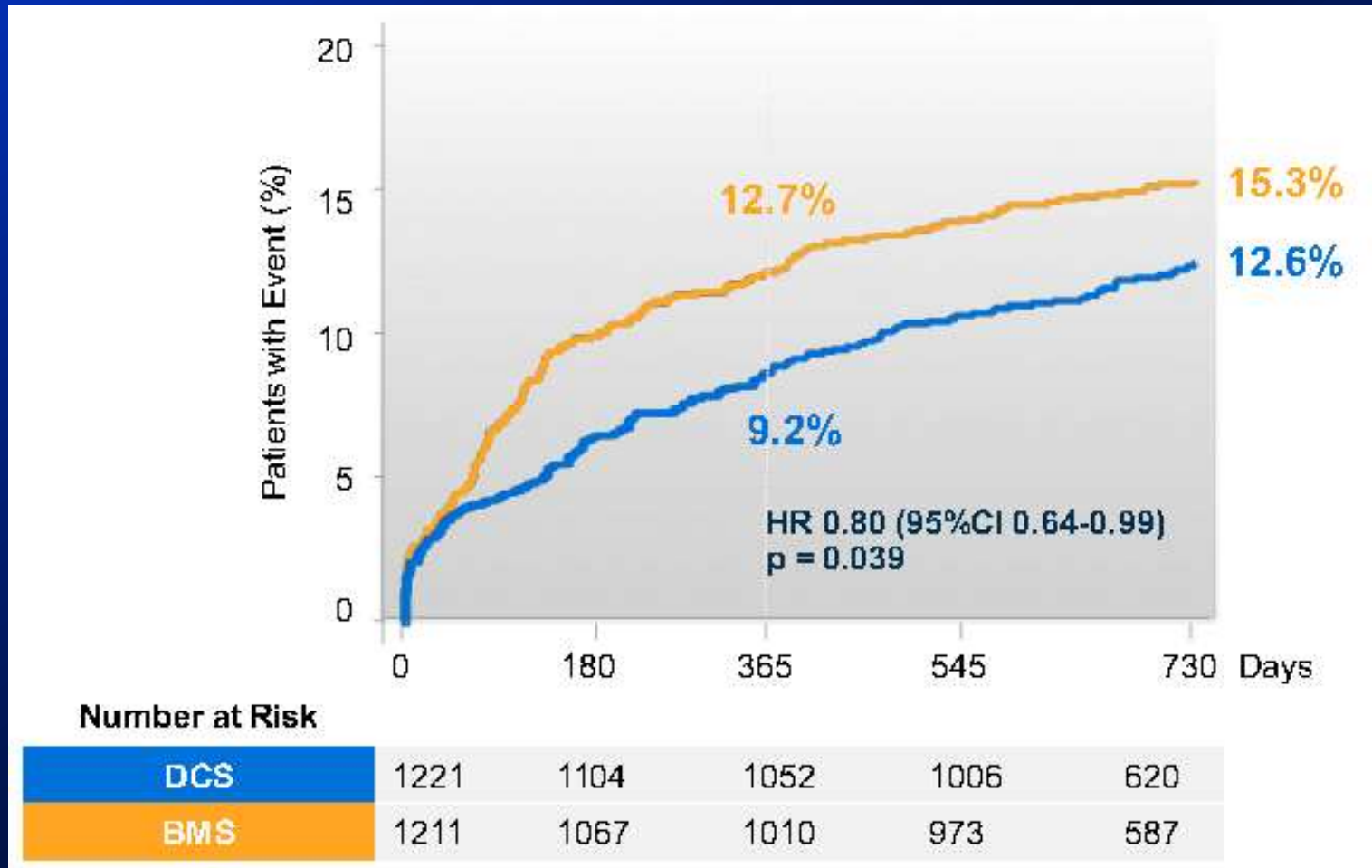
Components of safety end points at 2 years

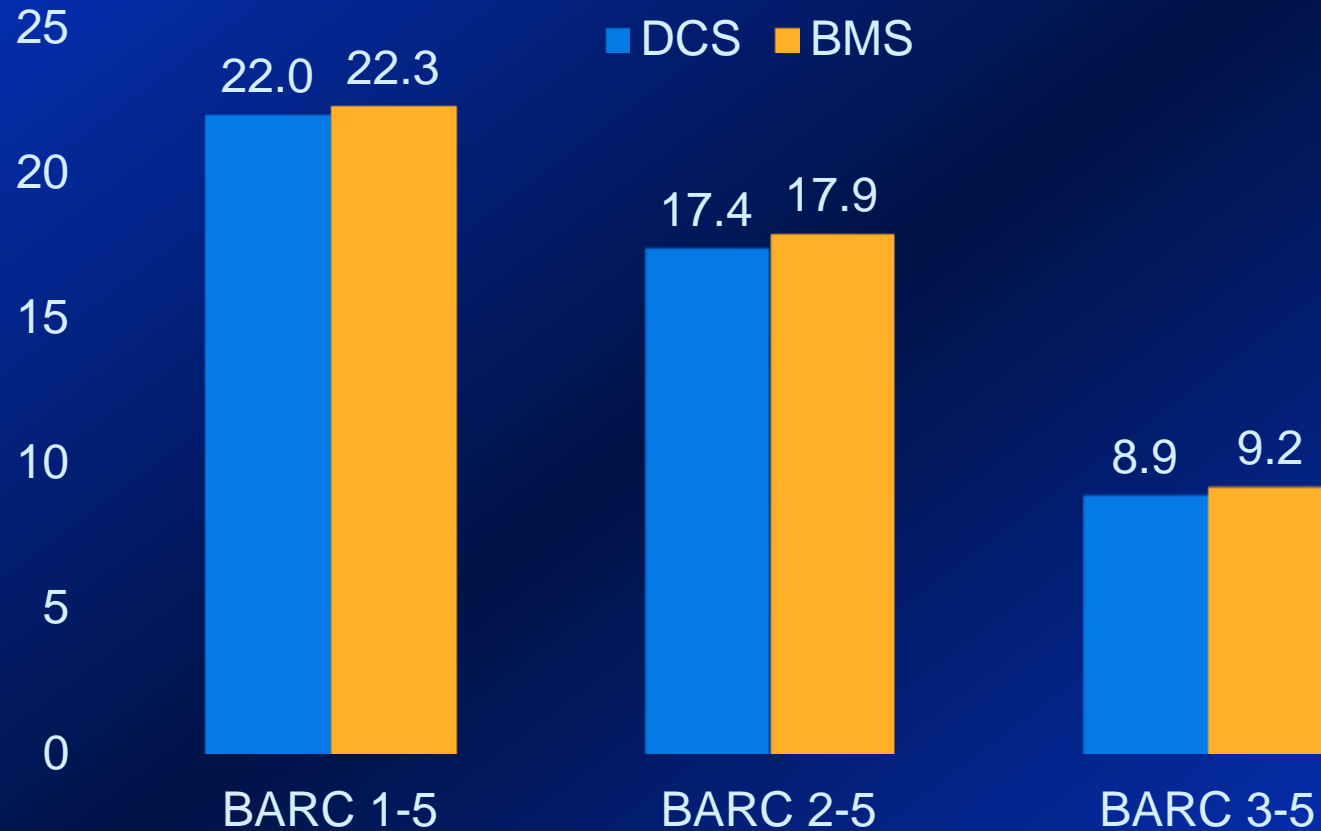Bar chart comparing DCS and BMS across three safety endpoints at 2 years:

Endpoint	DCS	BMS
Cardiac death	6.6	6.9
MI	7.4	10.1
ST (def / prob)	2.1	2.3

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Endpoints in a bit more detail …

Primary efficacy endpoint at 2 years (clinically driven TLR)

2 year FU was obtained at 730 days +60 days

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Were these patients really HBR?

Bleeding rates at 2 years follow-up

BARC I BARC 2 BARC 3 BARC 4 BARC 5

A – B - C

Bleeding that is not actionable and does not cause the patient to seek medical attention

Bleeding that requires medical attention and/or admission but not as bad as BARC 3

Bleeding with > 3gdl ↓in Hgb, needing transfusion, surgery or ICH or ocular bleeding

CABG related bleeding

Fatal bleeding

Bleeding Academic Research Consortium. *Circulation* 2011; 123 (23): 2736–47

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Illustrative Case

- 78 year old Chinese lady

- Admitted February 2015 with fever, crampy abdominal pain. Diagnosis – colitis, treated with IV antibiotics and discharged

- Hgb on admission 10.7 → 9.3 at discharge

- Presented one week later with acute anterior STEMI

- Primary PCI of the LAD performed with Biofreedom 3.0 x 33 mm DES → post dilated with 3.5 mm
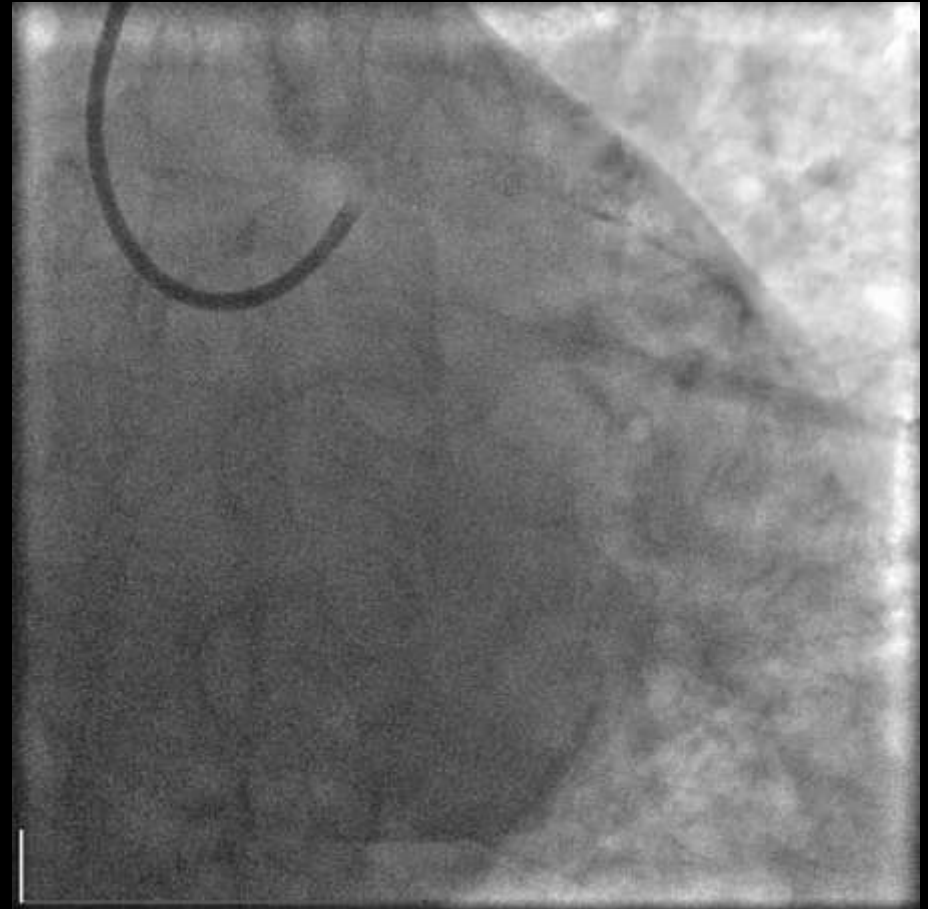
- Clopidogrel and aspirin

- PRE PCI
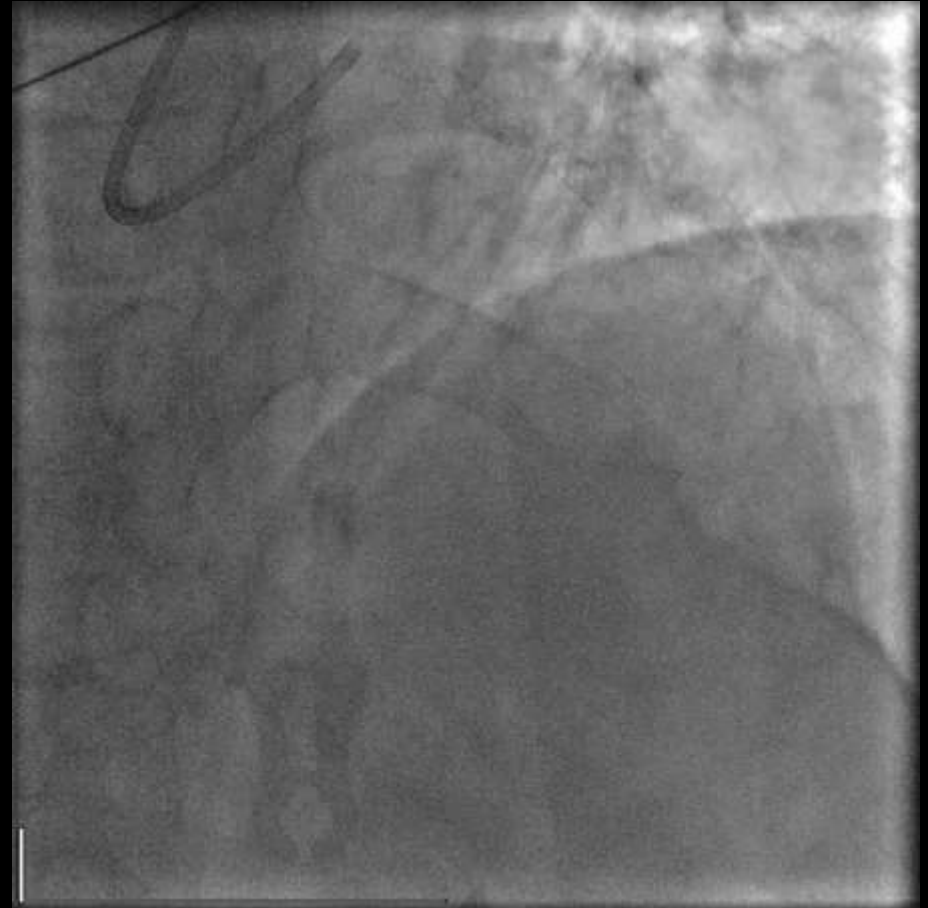
- POST PCI
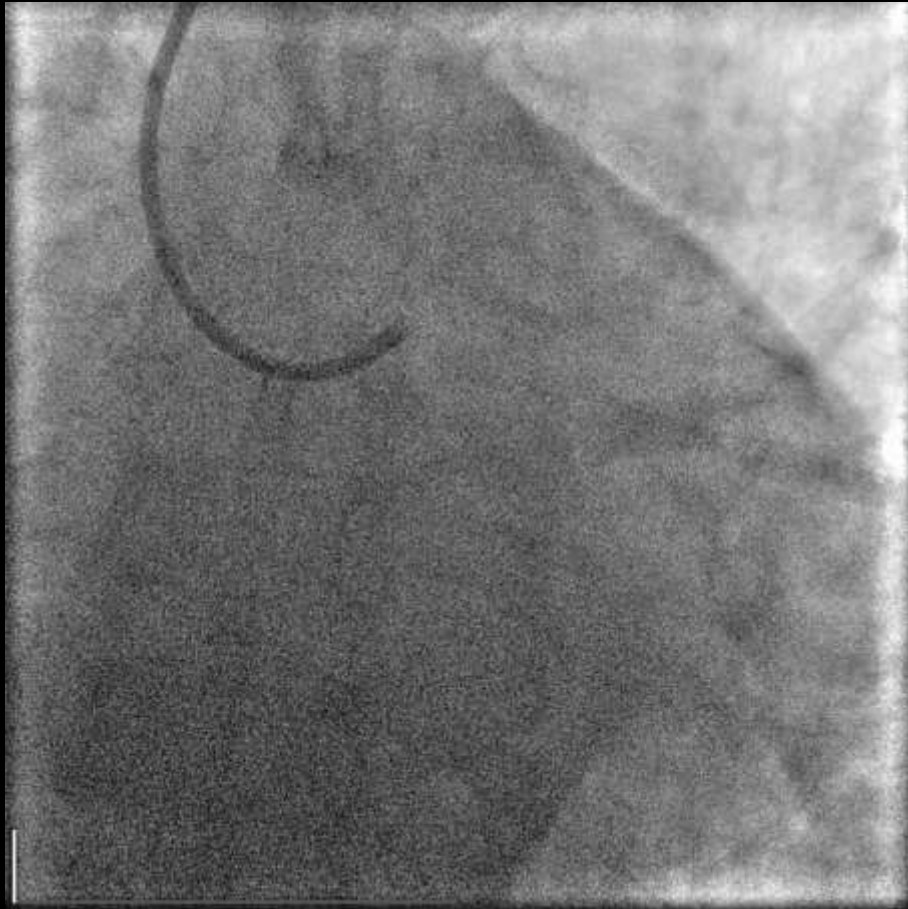
- PRE PCI
- POST PCI

Subsequent Course 1

- 2 days later developed acute intestinal obstruction
- CT → mass at splenic flexure
- Colonoscopy → mass confirmed →
  - STENTING of the splenic flexure by general surgery.
  - No biopsy as on DAPT
- Impression: likely malignancy needs surgery soon

Subsequent Course 2

- Readmitted 35 days following STEMI for elective surgery

- Clopidogrel stopped 5 days prior to day of admission

- Underwent uneventful hemicolectomy. Biopsy: MALIGNANCY but localized

- Patient still well 2 years later

Conclusions

- At 2 years → BA9 coated stent treated with one month of DAPT was
  - SAFER than a bare metal stent
  - MORE EFFICACIOUS than a bare metal stent
- No subgroup identified where use of a BMS was superior
- HBR patients are difficult
  - Persistently high incidence of bleeding and thrombotic events
  - Accounts for high mortality
- Identification of predictors of the composite primary safety EP and major bleeding may help design future trials of DAPT duration in HBR patients