



6/7/8
JUN 2018
BIARRITZ



Lessons learnt from **LEADERS** *FREE*

Philip Urban, Geneva, Switzerland

LESSONS LEARNT FROM LEADERS FREE

- Background
- LEADERS FREE at 1 and 2 years
- ACS presentation
- Need for long term oral anticoagulants
- Complex PCI
- What next?



2010: relative contraindications to DES

ESC 2010 guidelines

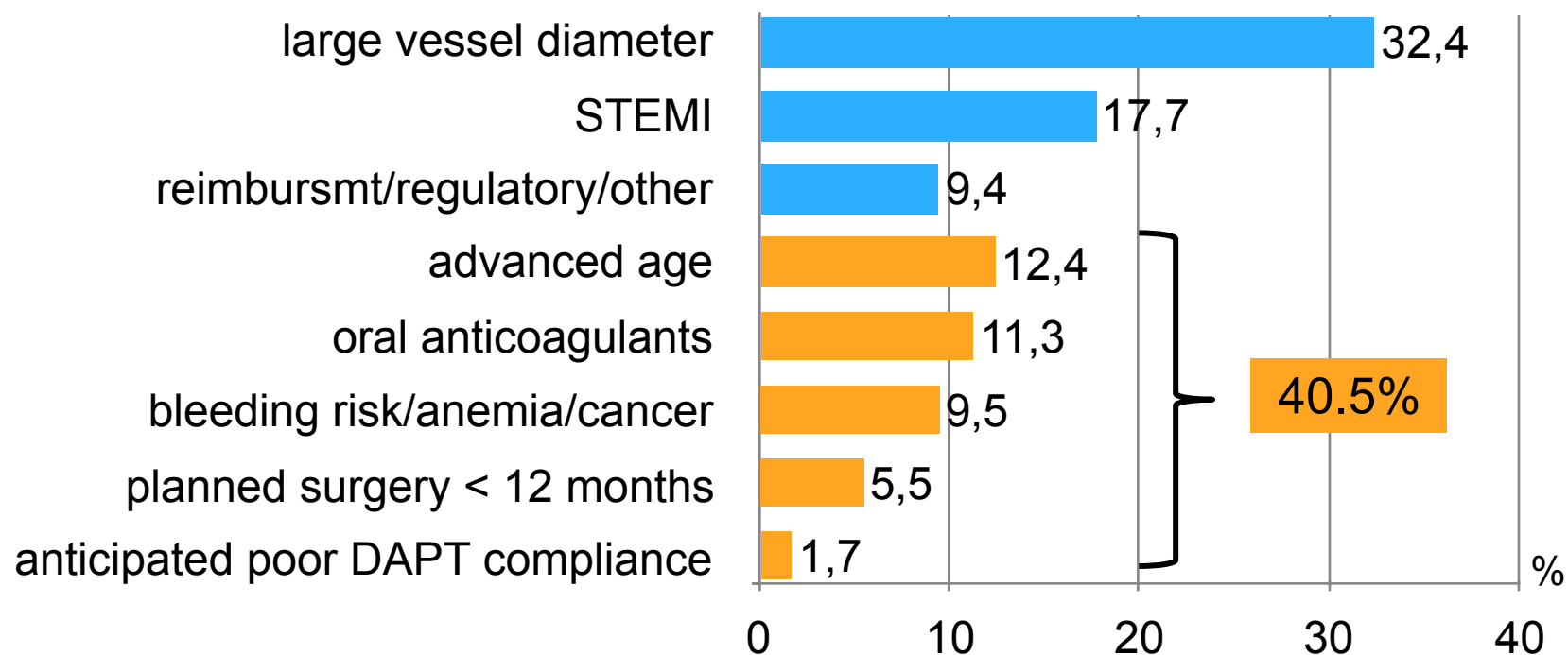
- | |
|---|
| • Clinical history difficult to obtain, especially in the setting of acute severe clinical conditions (STEMI or cardiogenic shock). |
| • Expected poor compliance with DAPT, including patients with multiple comorbidities and polypharmacy. |
| • Non-elective surgery required in the short term that would require interruption of DAPT. |
| • Increased risk of bleeding. |
| • Known allergy to ASA or clopidogrel/prasugrel/ticagrelor. |
| • Absolute indication for long-term anticoagulation. |

BMS registry - April 9 to May 15, 2012

33 European/Asian centres

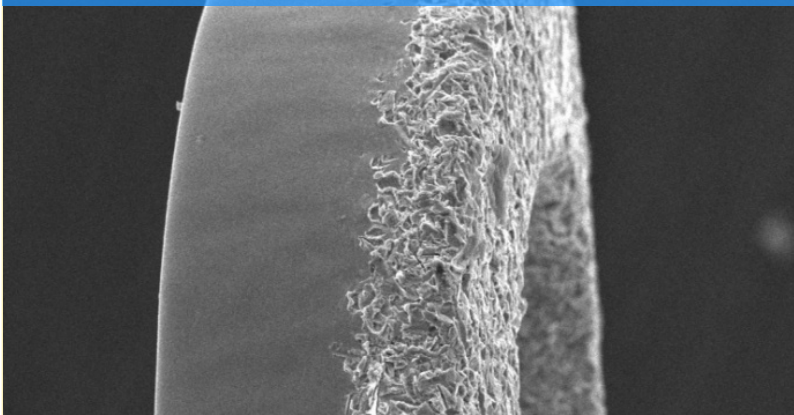
744 consecutive patients treated with BMS

Single main reason for using a BMS

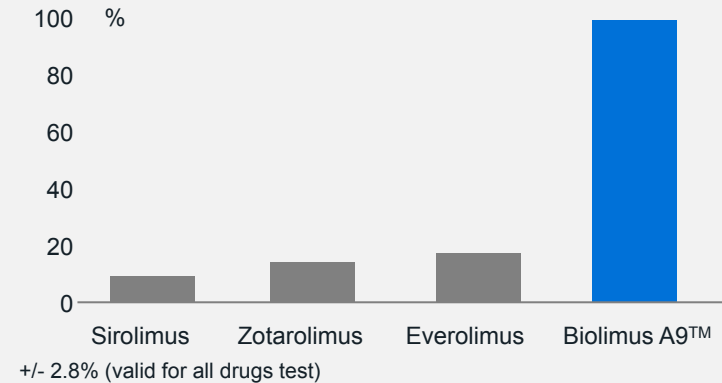


BioFreedom™ Drug Coated Stent (DCS)

Selectively Micro-Structured Surface Holds Drug in Abluminal Surface Structures



BA9™ Drug 10 Times More Lipophilic than Sirolimus¹

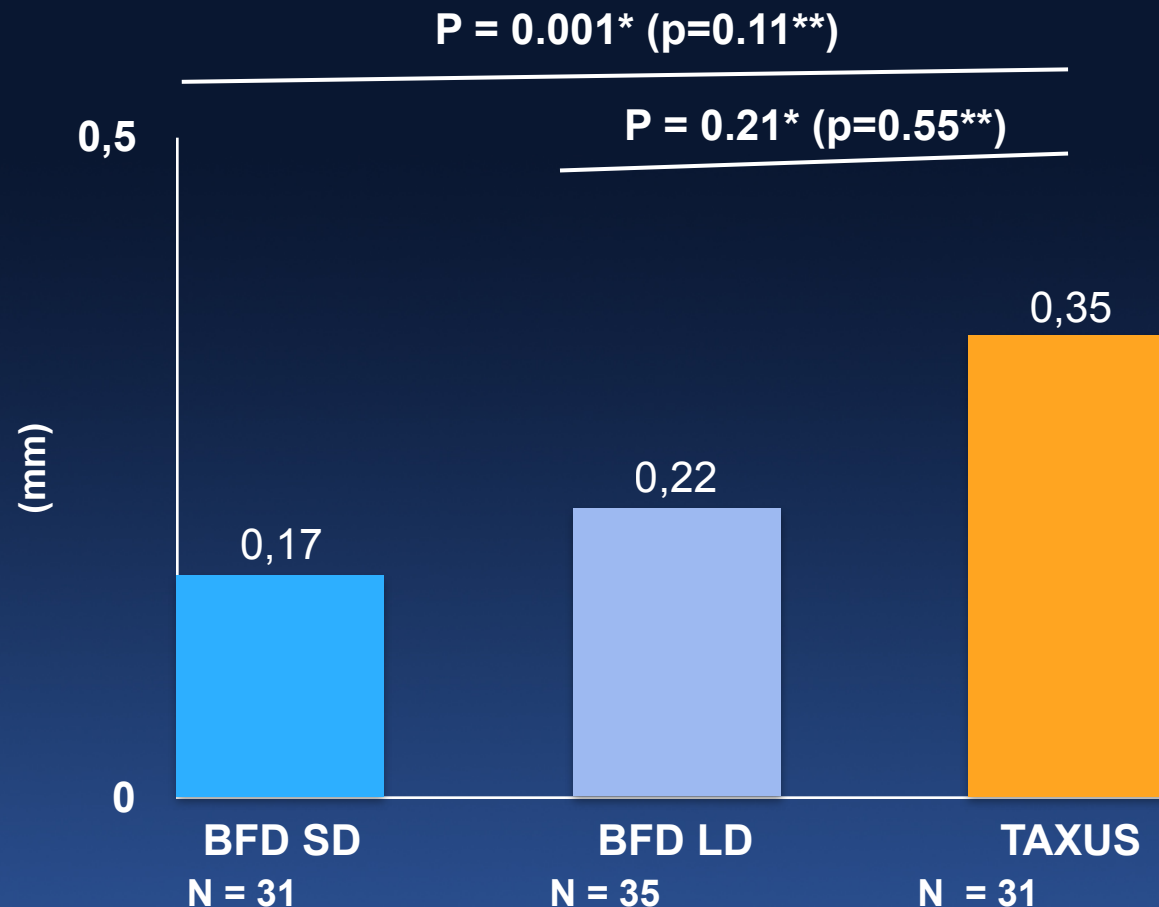


Advantages:

- Avoid any possible polymer-related adverse effects
- Rapid drug transfer to vessel wall (98% within one month²)
- Good fit with short DAPT

FIM: In-Stent LLL at 12-month Follow-up

2nd Cohort – Primary Endpoint



LEADERS FREE Trial Design

Prospective, double-blind randomized (1:1) trial
2466 High bleeding risk (HBR) PCI patients

BioFreedom™
DCS

vs.

Gazelle™
BMS

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

- Primary safety endpoint:
Composite of cardiac death, MI, definite / probable stent thrombosis at 1 year (non-inferiority then superiority)
- Primary efficacy endpoint:
Clinically-driven TLR at 1 year (superiority)



Didier Carrié

CHU Toulouse Rangueil - France

65 years-old man

NSTEMI Troponin +

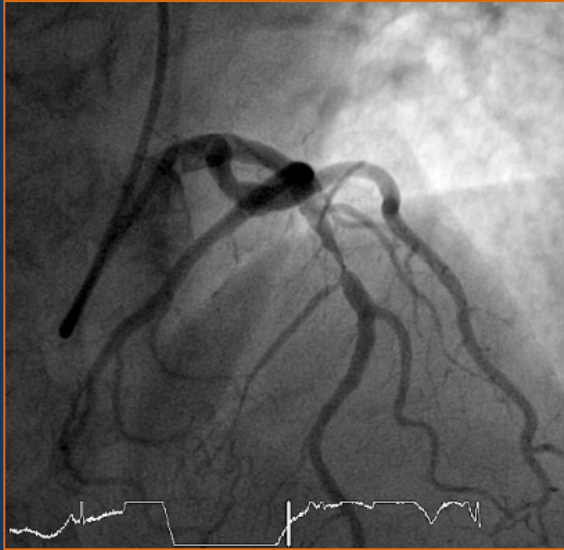
EKG: negative T waves in anterior leads

Risk factors: HTA, smoking, hypercholesterolemia, BMI:31

➔ Rendu-Osler : hereditary hemorrhagic telangiectasia

Included because of: « expected poor compliance with DAPT for other medical reasons »





Brain MRI to exclude
AV malformation
(≈frequent in HHT)



PCI of mid-LAD
Leaders Free stent
4.0 X 18mm



Day 22: epistaxis +++
Visit to Emergency department
Hb level: 9,3 g/dl
No blood transfusions
No angina

Decision: DAPT for 8 days more, then aspirin alone

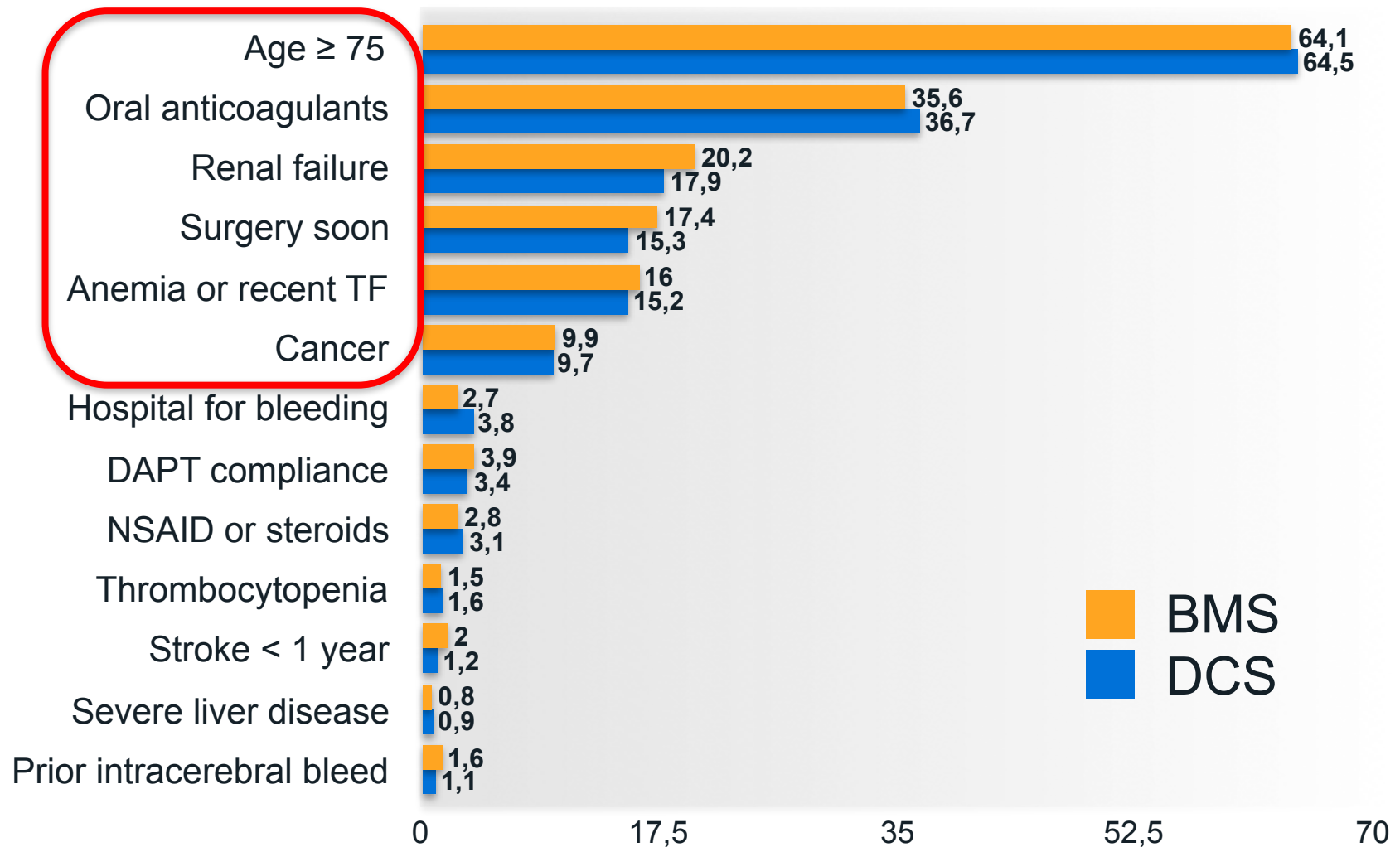
FU: did well on ASA alone, with occasional minor nose bleeds.

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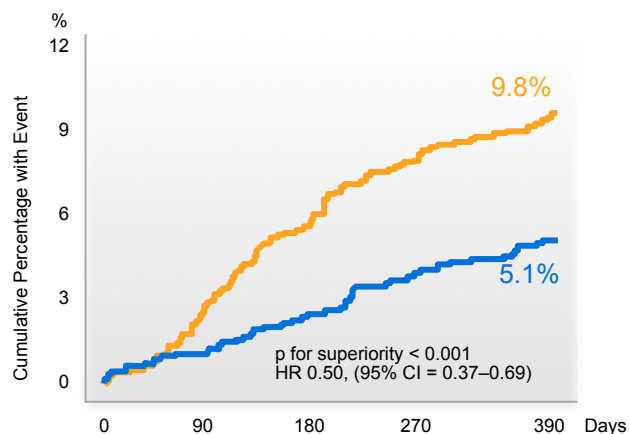
Inclusion Criteria Applied (1.7 criteria / patient)



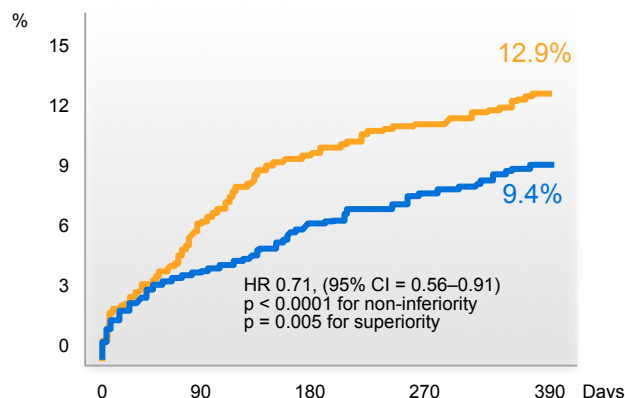
Primary Endpoints and Major Bleeding at 1 Year

DCS BMS

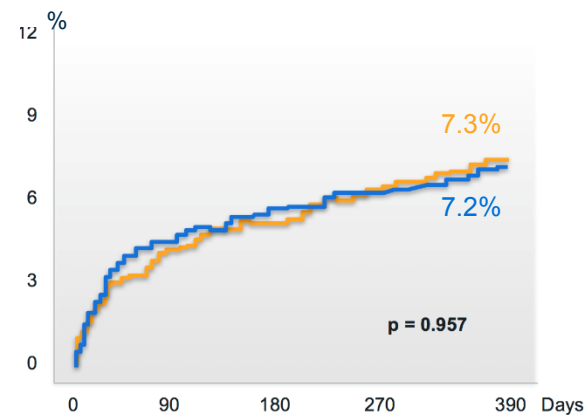
Efficacy (cd-TLR)



Safety (cardiac death, MI, ST)

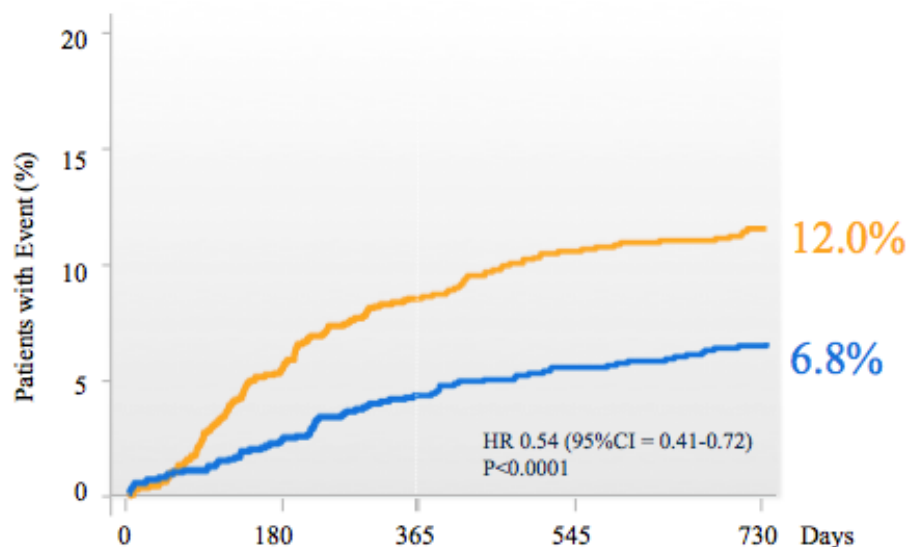


Bleeding (BARC 3-5)

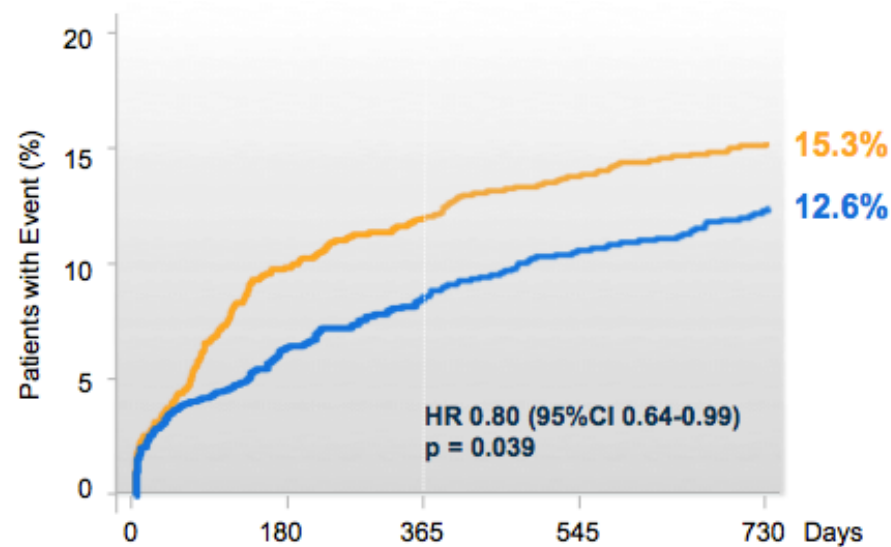


Efficacy and Safety Endpoints @ 2 Years

Efficacy (cd-TLR)

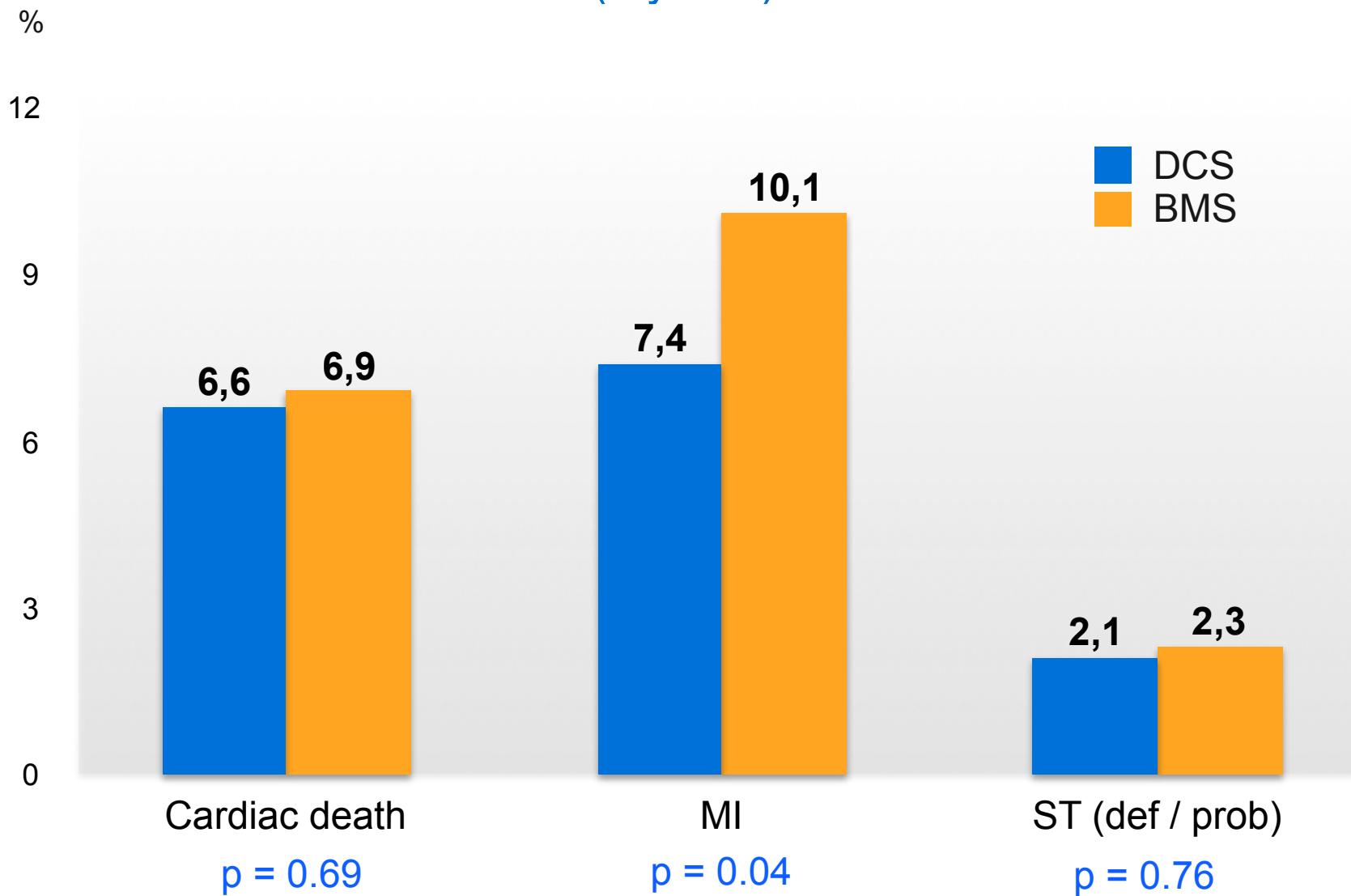


Safety (cardiac death, MI, ST)

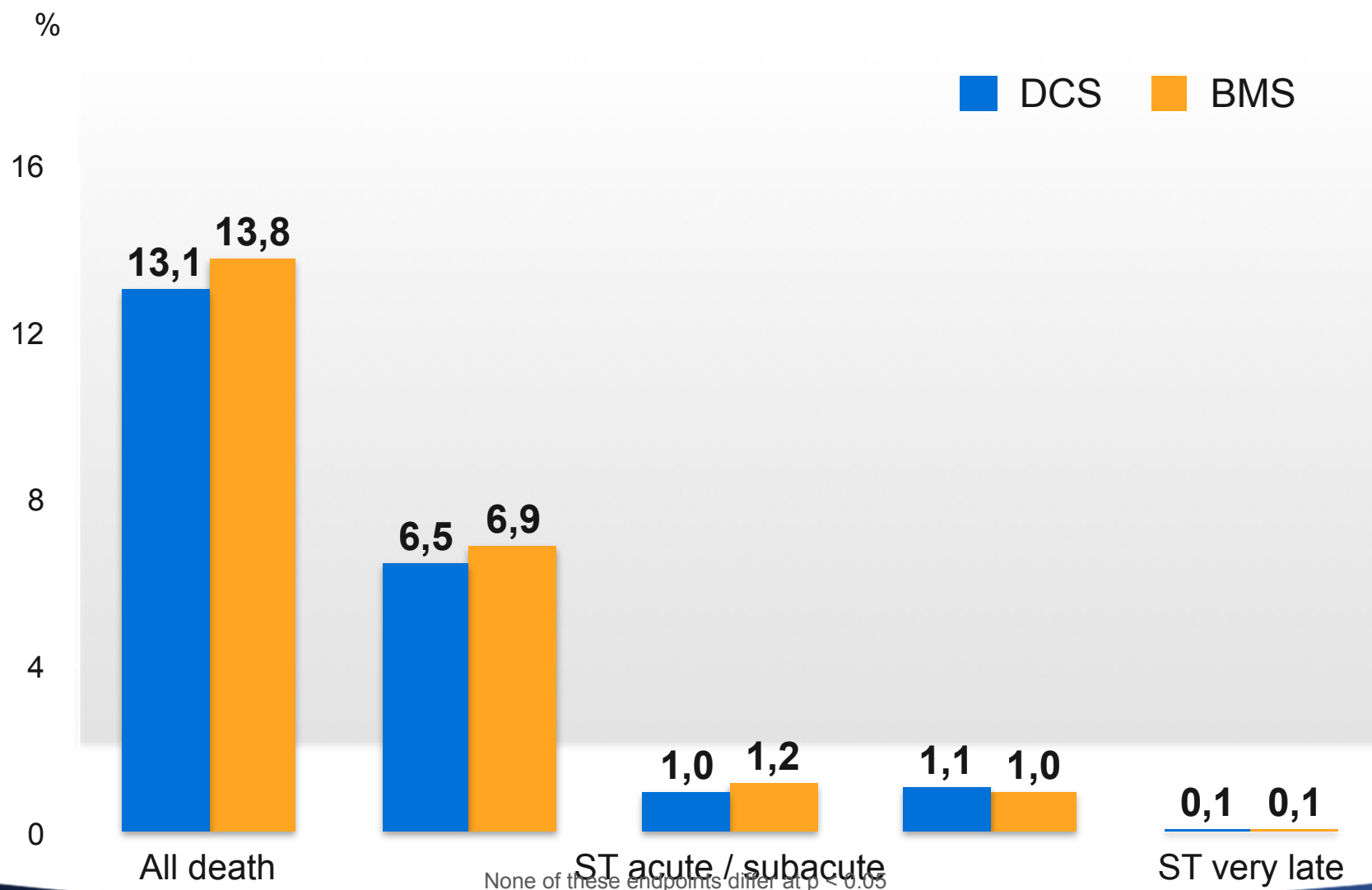


2 year FU was obtained at 730 days $\pm$ 60 days

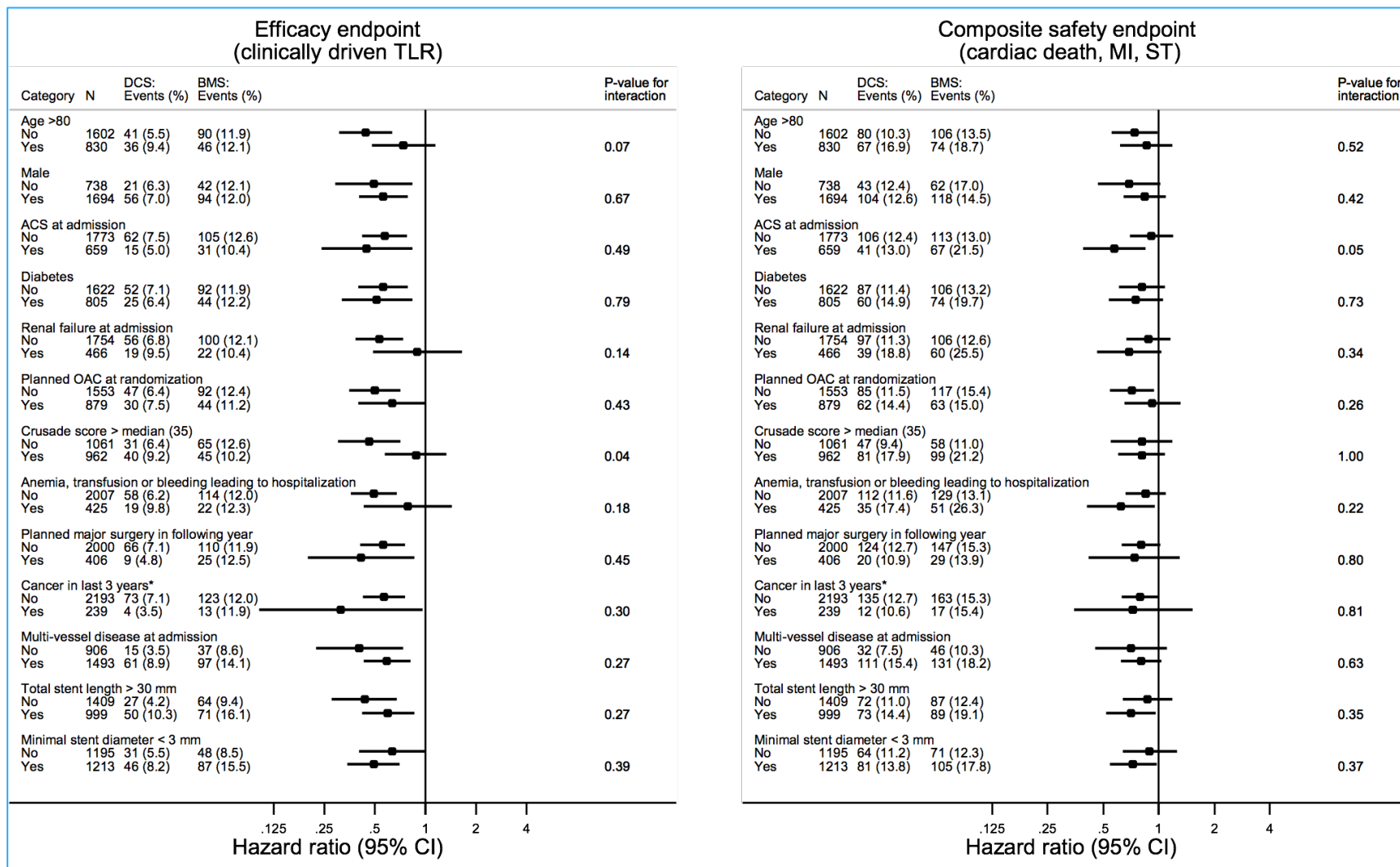
Components of Safety Endpoint (2 years)



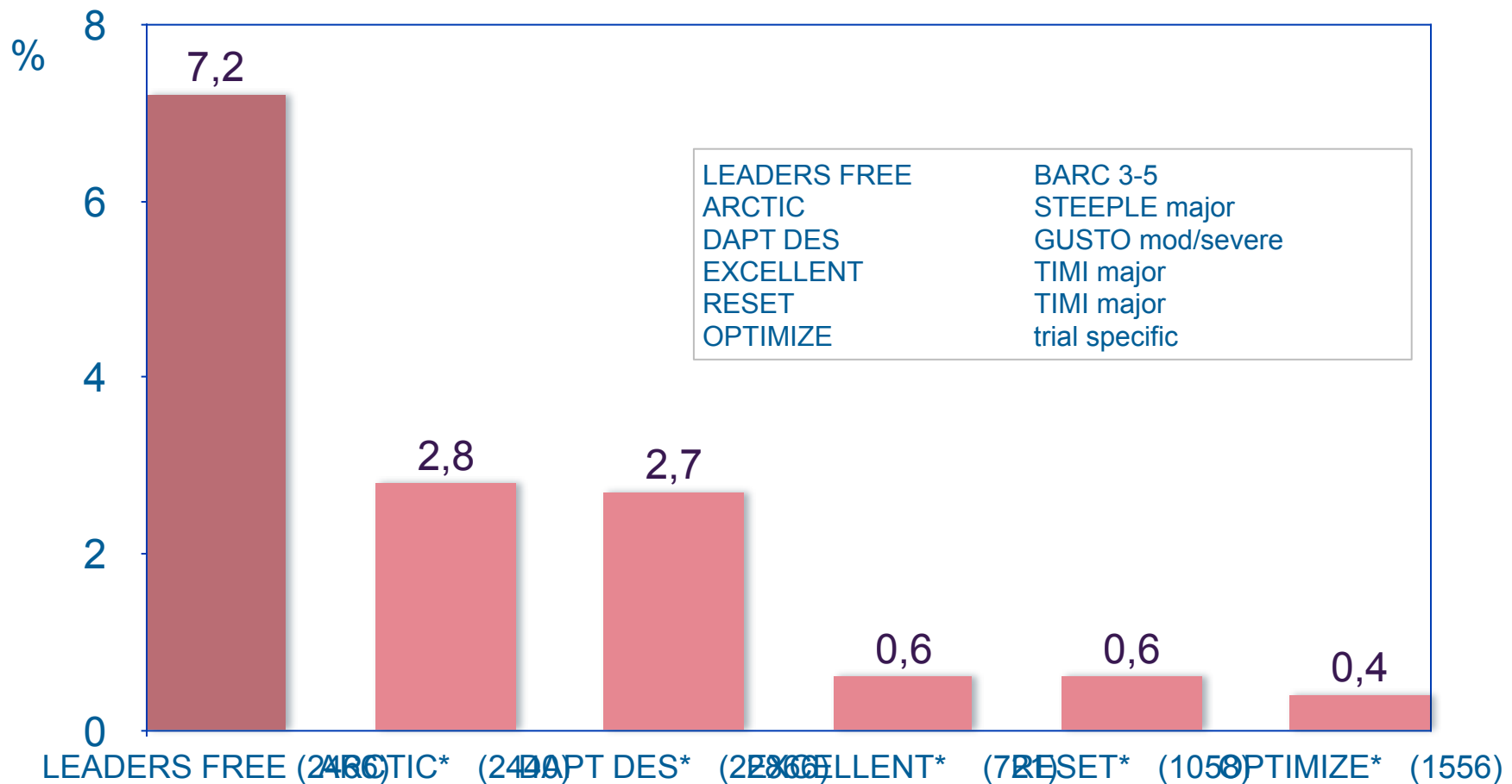
Selected Secondary Safety Endpoints (2 years)



Subgroups at 2 years follow-up



Major bleeding during first year



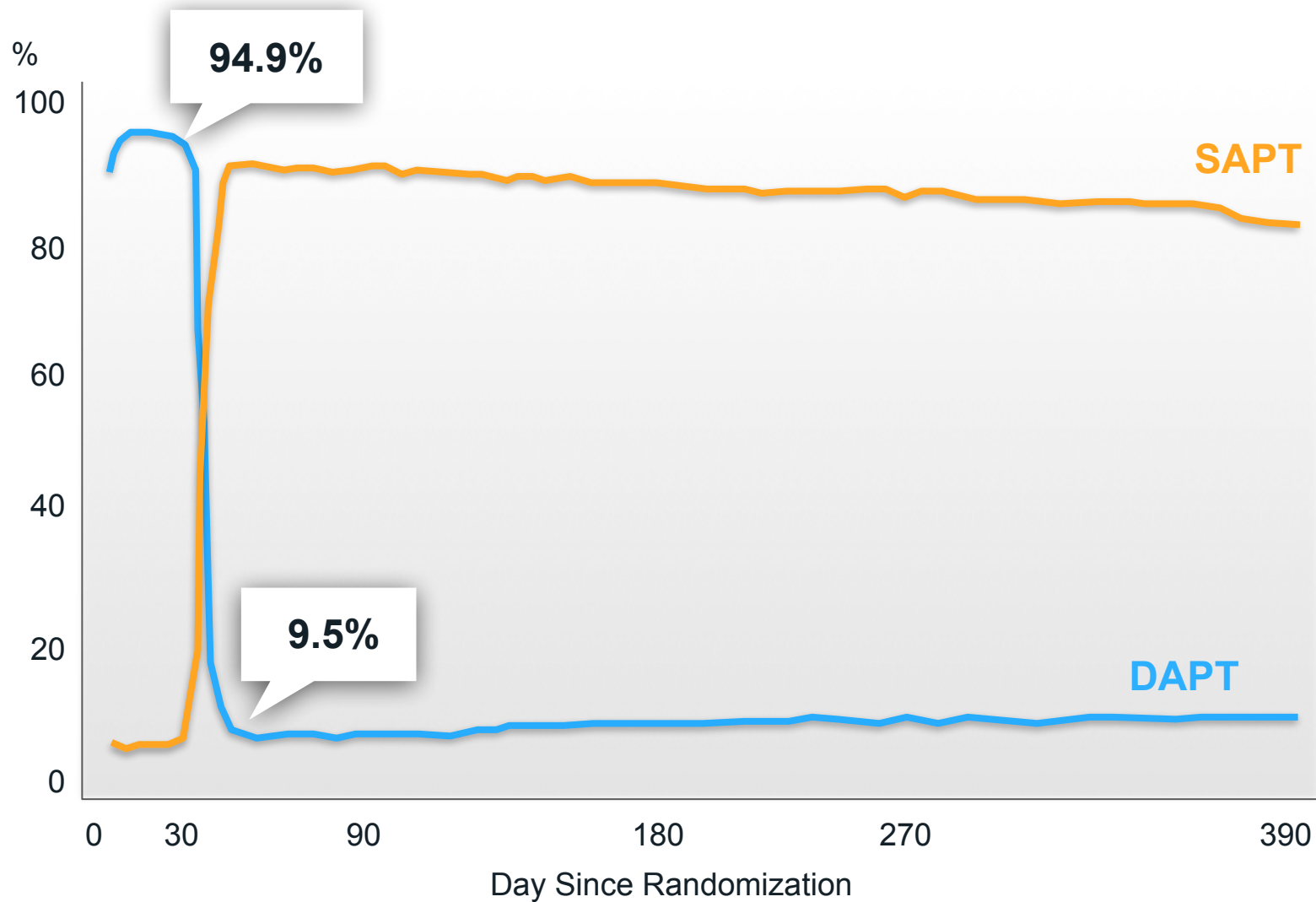
*on DAPT for first 12 months after PCI

DAPT trials exclusion criteria (✗) vs. LEADERS FREE inclusion criteria (✓)

	EXCELLENT	RESET	ARCTIC	OPTIMIZE	DAPT DES	LEADERS FREE
Low Hb or thrombocytopenia	✗	✗				✓
Recent bleeding	✗	✗	✗			✓
Anticoagulants	✗		✗	✗	✗	✓
Need for surgery	✗		✗	✗	✗	✓
Renal or hepatic failure	✗	✗				✓
STEMI and/or GP 2b3a blockers	✗		✗	✗		not excluded
Anticipated difficulties with long term DAPT	✗	✗	✗		✗	✓

Antithrombotic medication

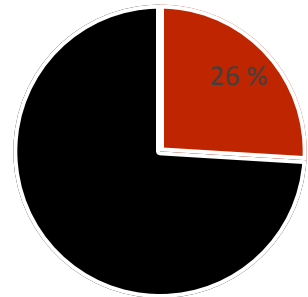
DAPT During Follow-Up



DAPT= dual antiplatelet treatment or clopidogrel alone + vitamin K antagonist during first 30 days

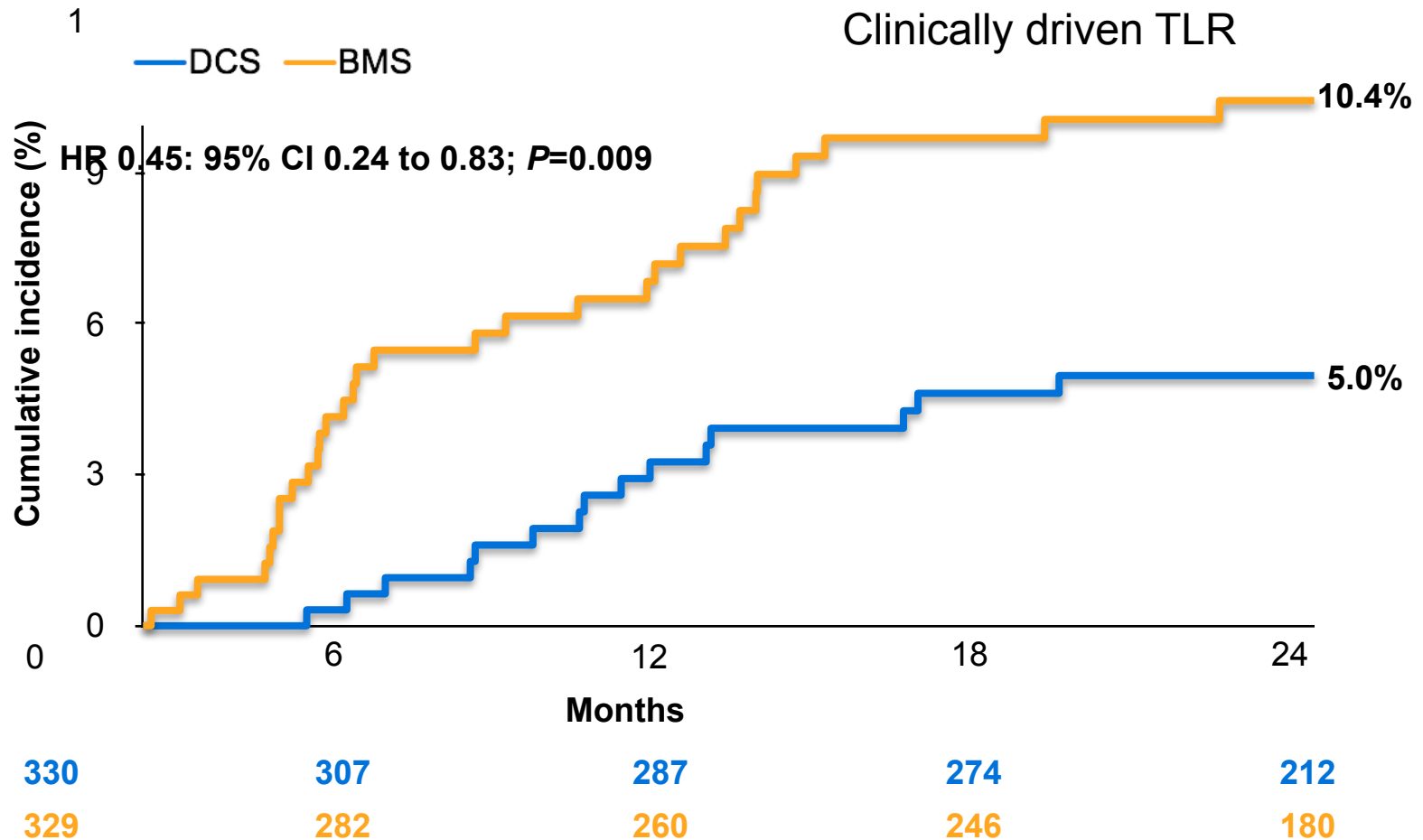
LESSONS LEARNT FROM LEADERS FREE

- Background
- LEADERS FREE at 1 and 2 years
- **ACS presentation (n=659)**
- Need for long term oral anticoagulants
- Complex PCI
- What next?



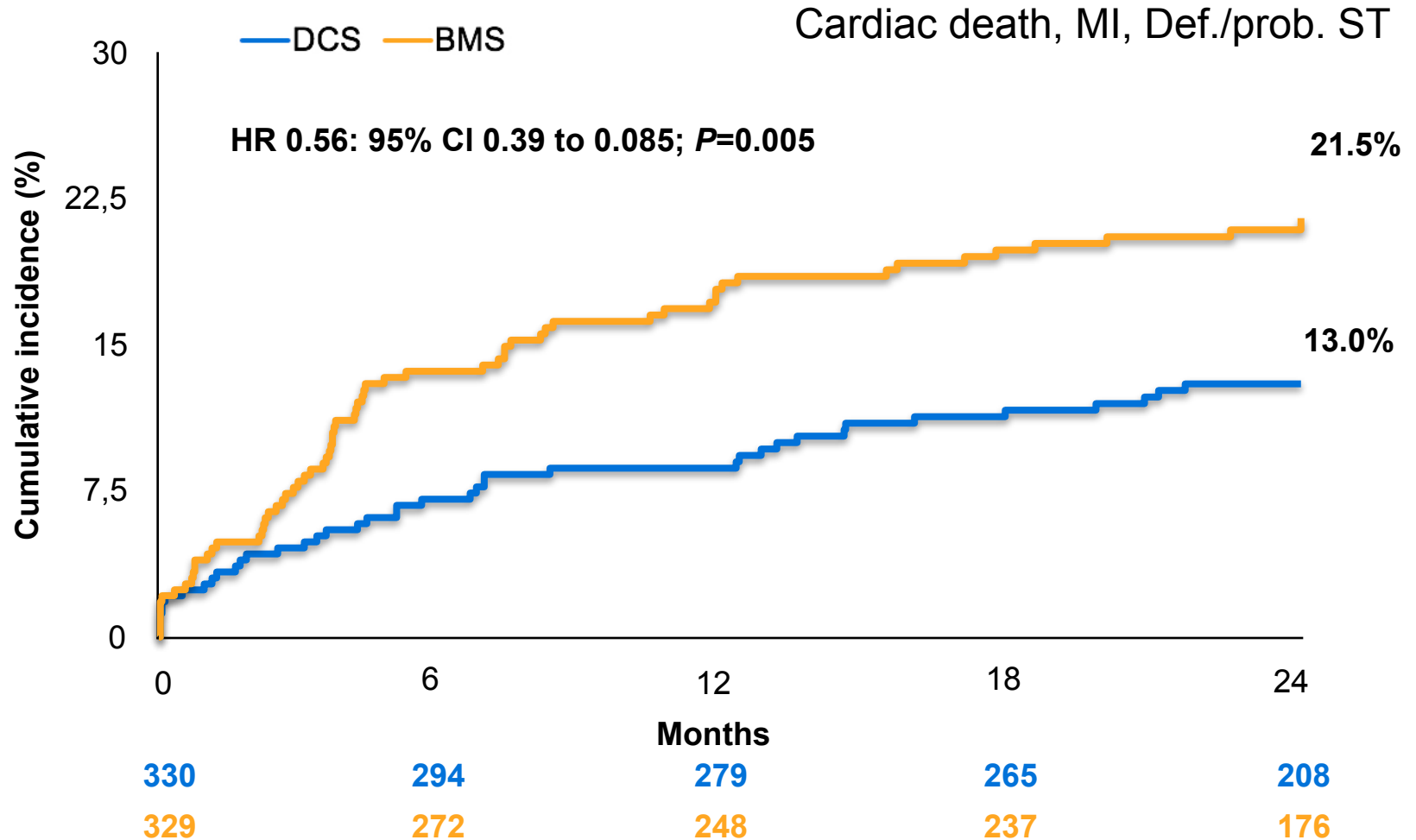
Leaders Free ACS

Primary Efficacy Endpoint at 2 years



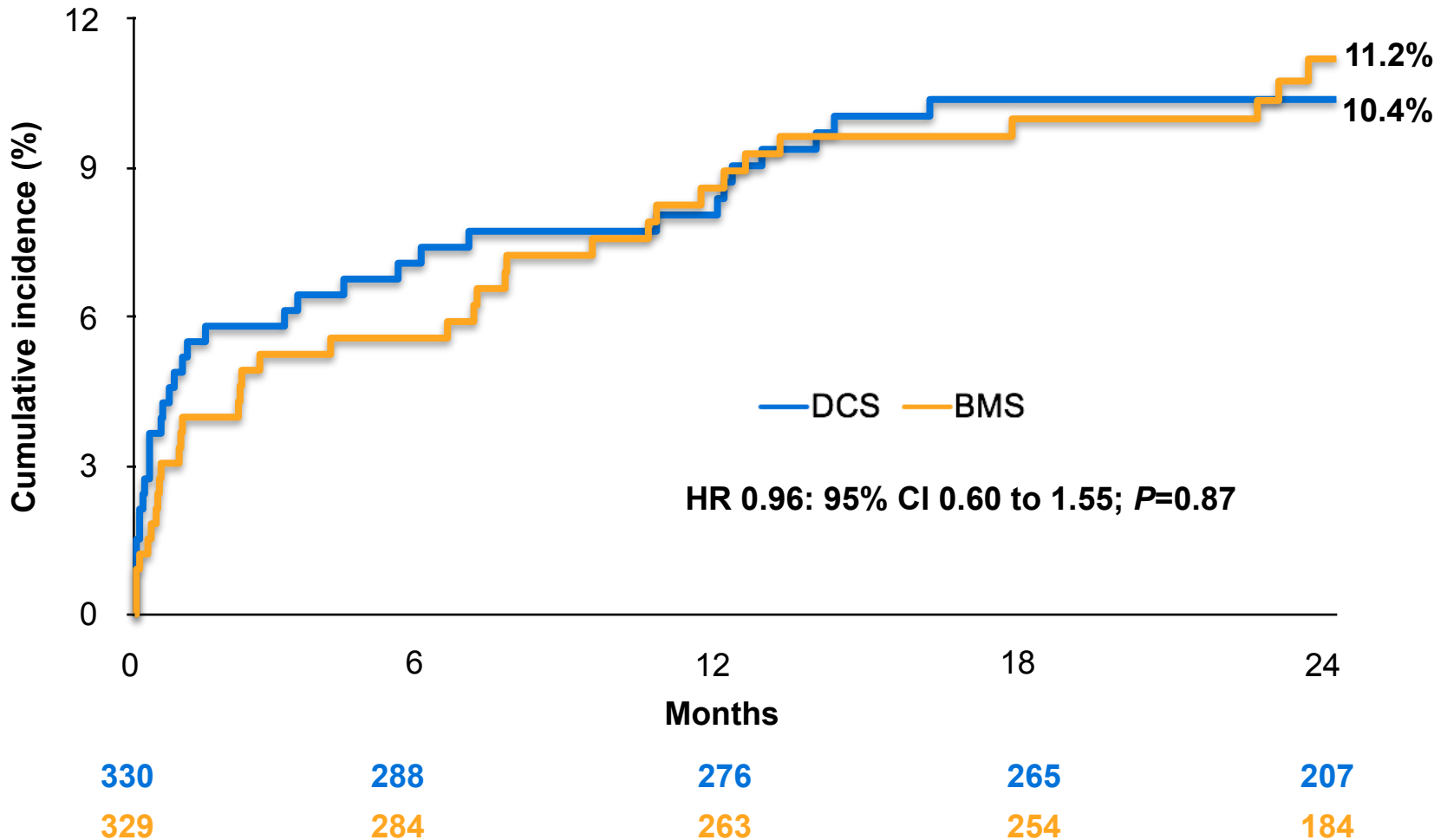
Leaders Free ACS

Primary Safety Endpoint at 2 years

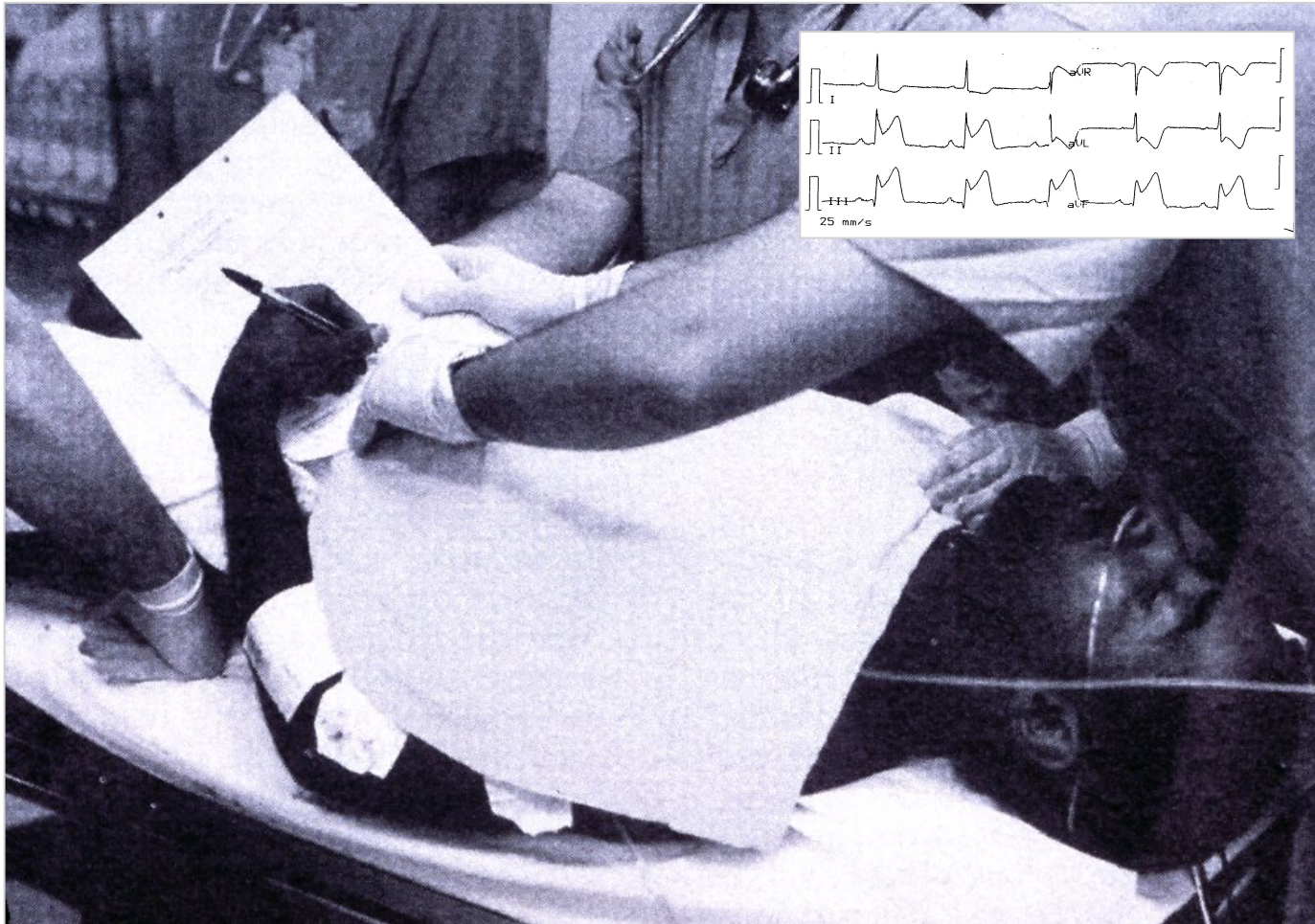


Leaders Free ACS

Major Bleeding at 2 years

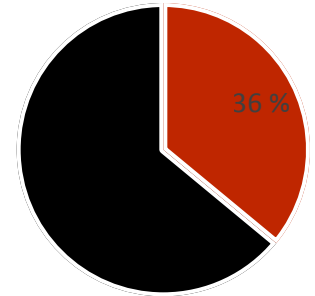


Detailed medical history?
Lab values?

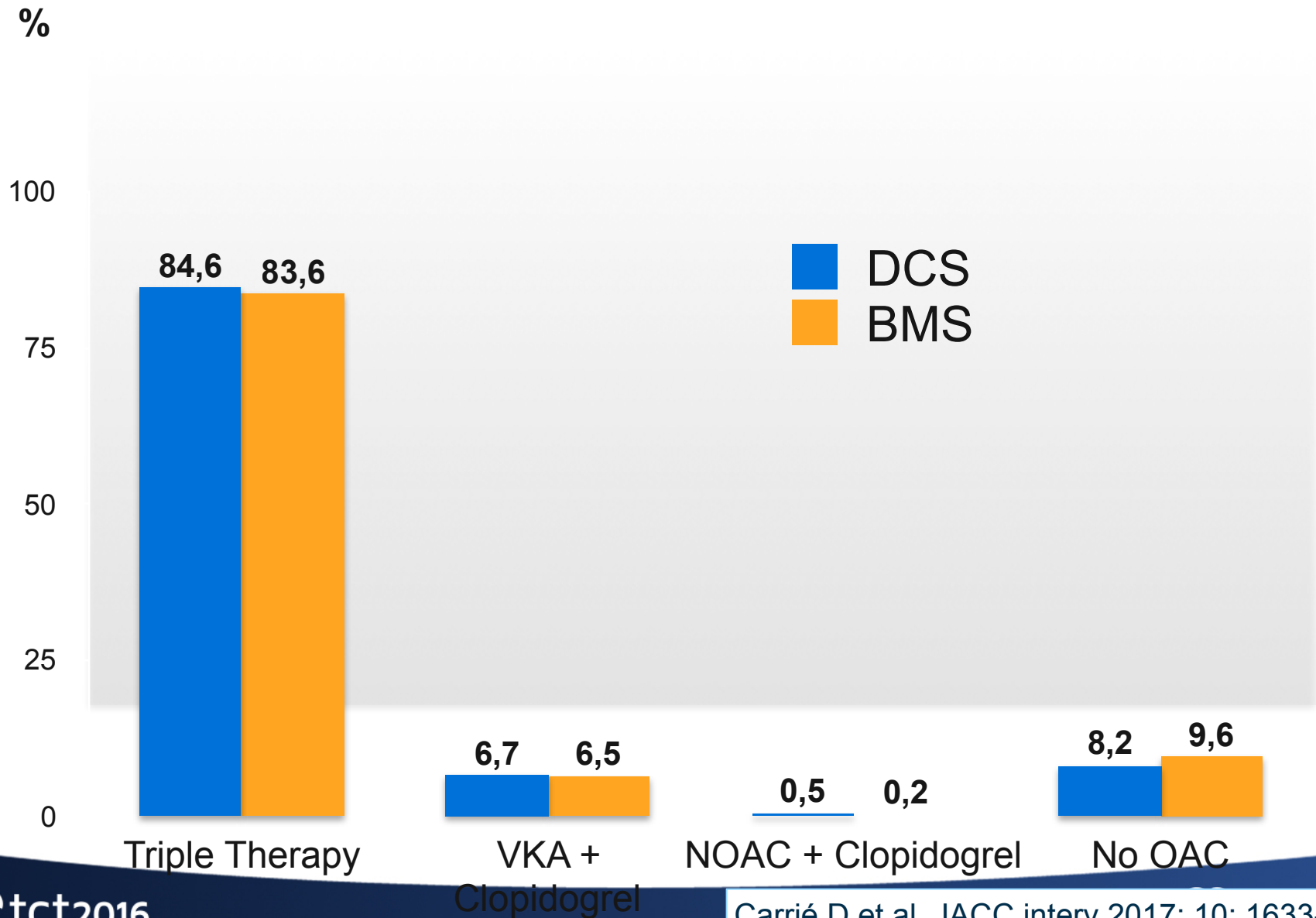


LESSONS LEARNT FROM LEADERS FREE

- Background
- LEADERS FREE at 1 and 2 years
- ACS presentation
- Need for long term oral anticoagulants (n=879)
- Complex PCI
- What next?



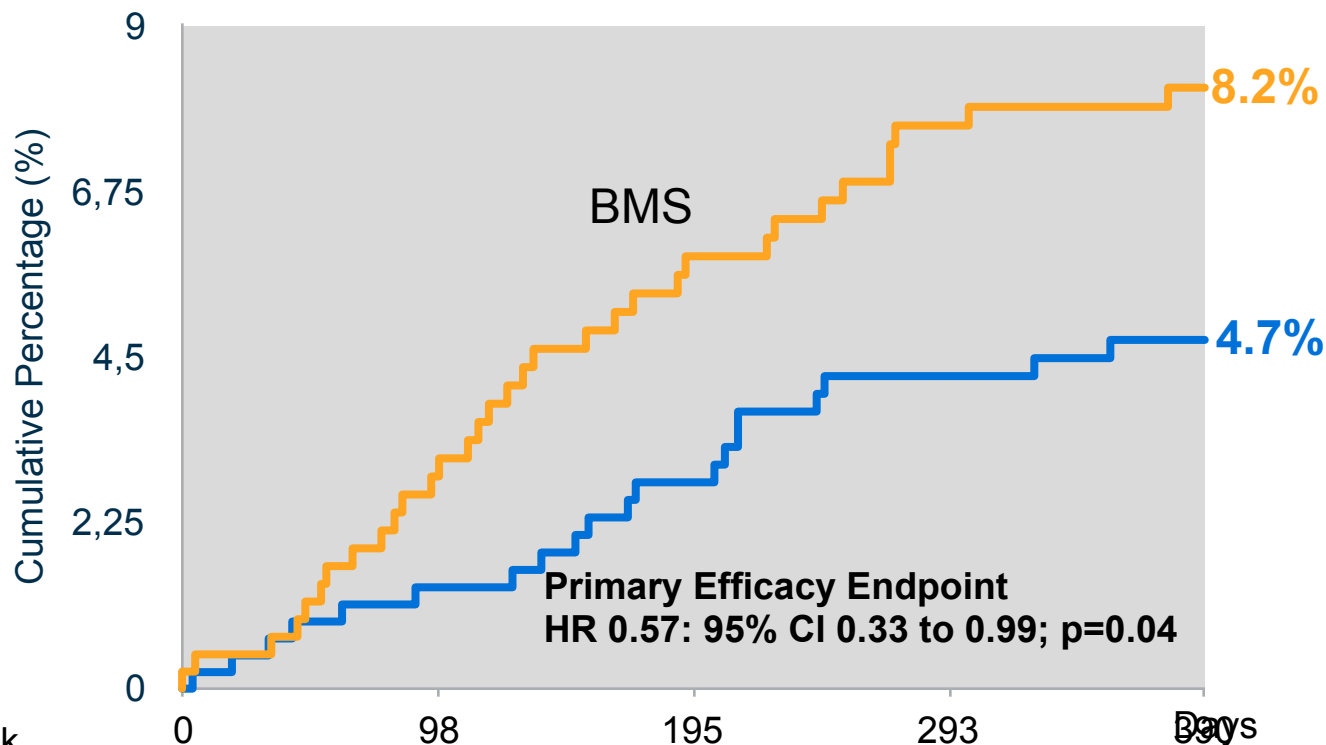
Antithrombotic Medication at Discharge



Leaders Free - planned OAC

(Primary Efficacy Endpoint)

Clinically-driven Target Lesion Revascularization – 1 Year FU



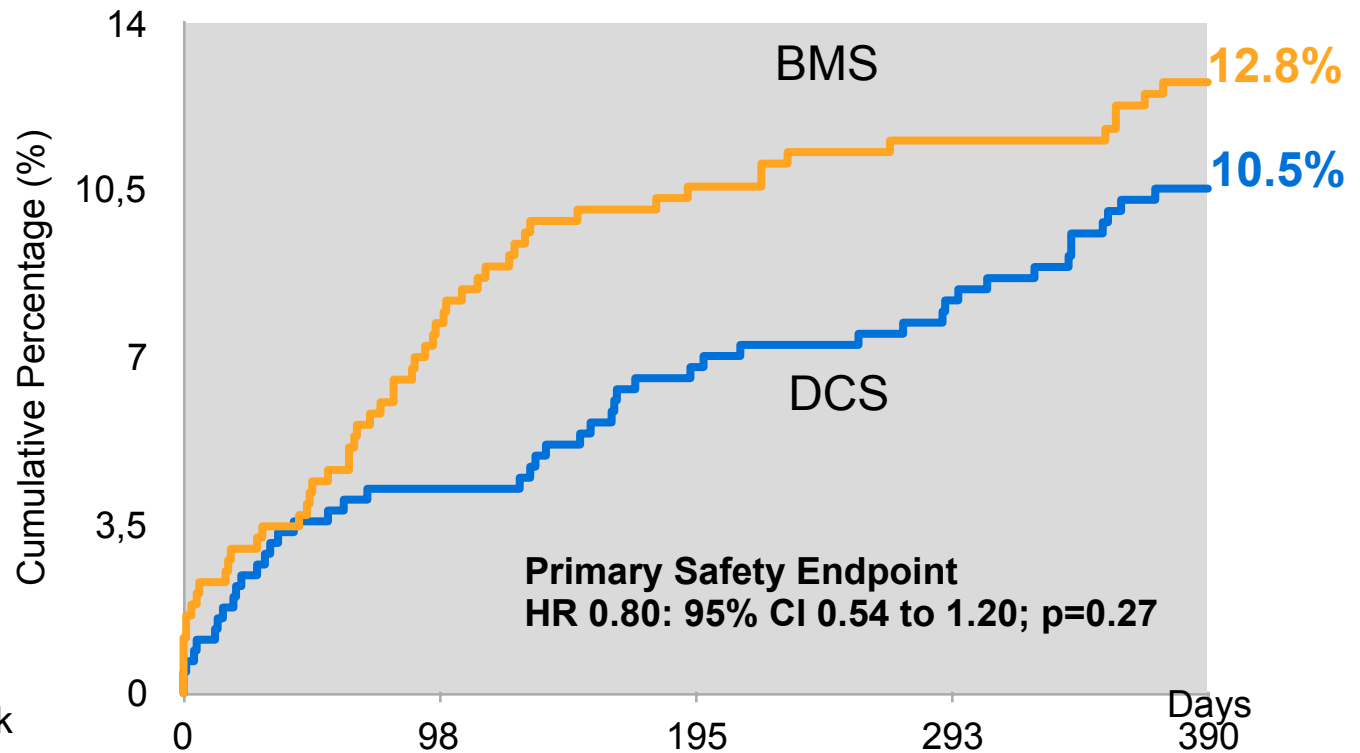
Patients at Risk

DCS	431	395	377	367	352
BMS	448	424	408	397	381

Leaders Free OAC

(Primary Safety Endpoint)

Cardiac Death, MI, or Def / Prob ST- 1 Year FU

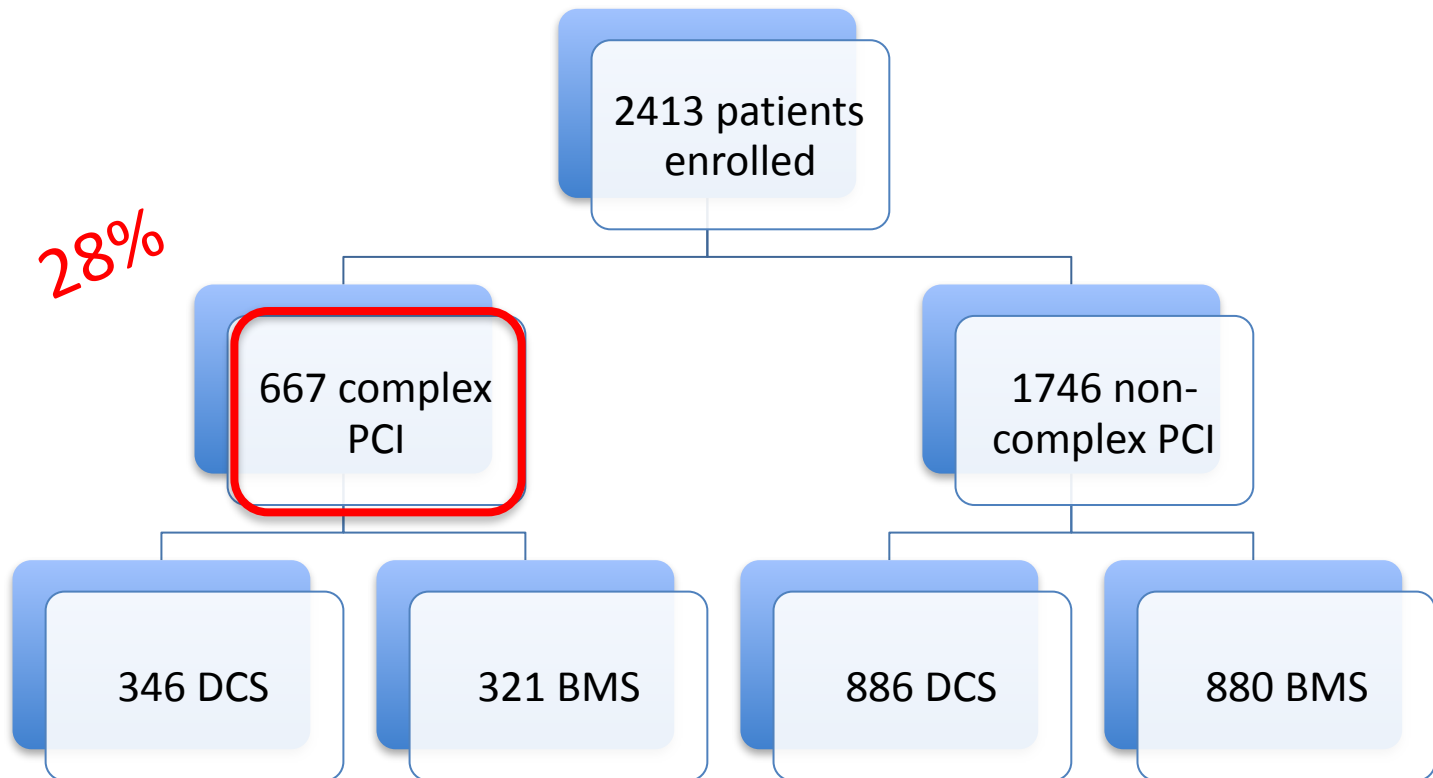


LESSONS LEARNT FROM LEADERS FREE

- Background
- LEADERS FREE at 1 and 2 years
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- Need for long term oral anticoagulants
- **Complex PCI**
- What next?

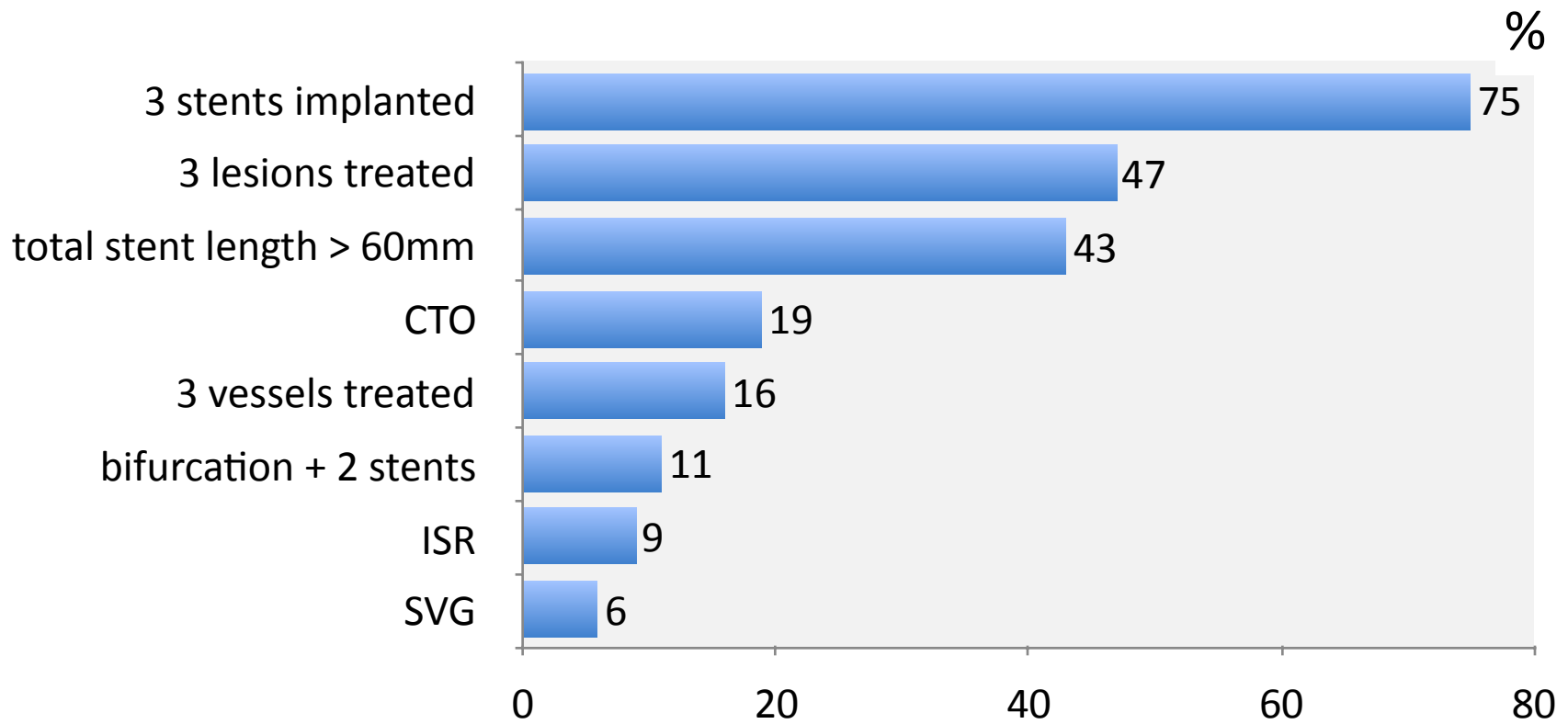


LEADERS FREE complex PCI



LEADERS FREE complex PCI

Diagnostic criteria for 667 complex PCI (one or more)

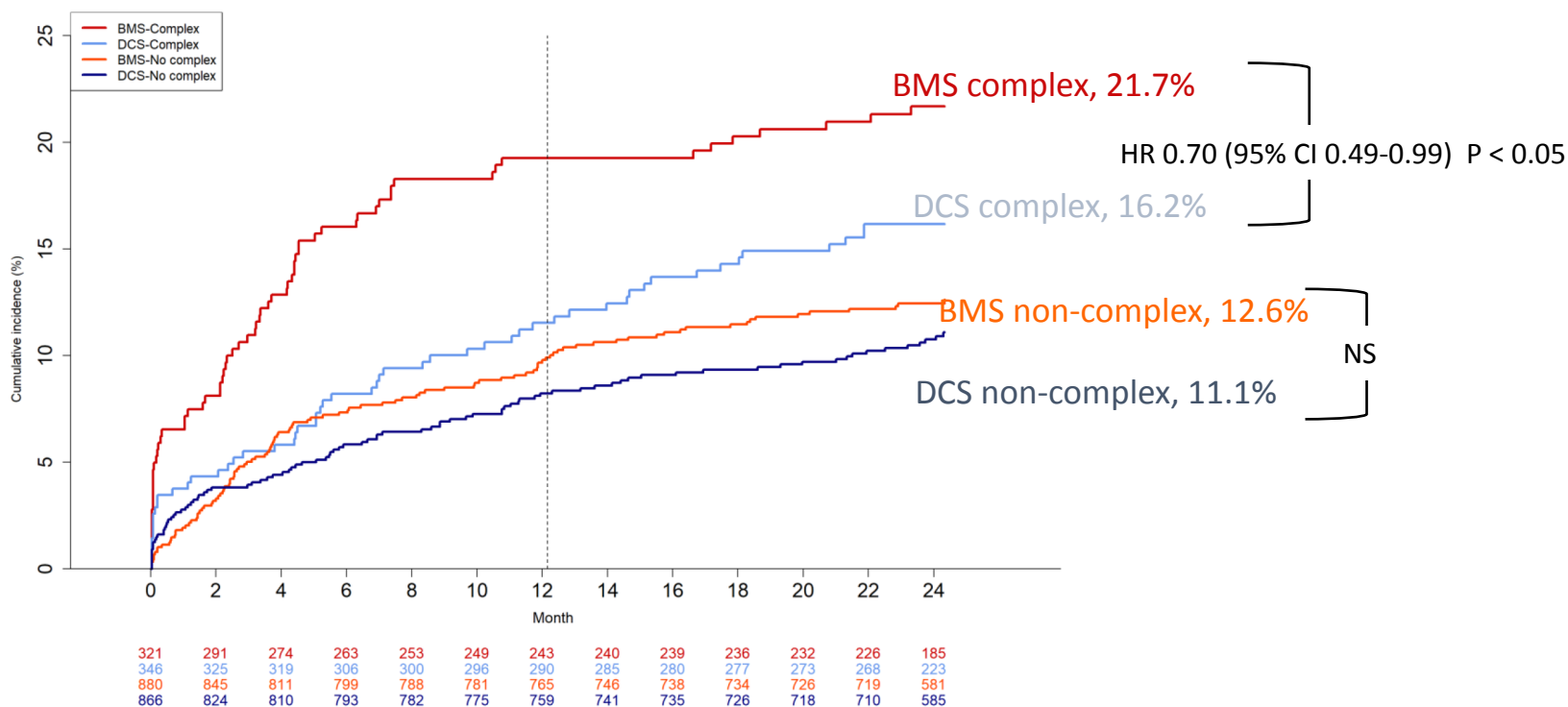


If none of the above, PCI was considered «non-complex»

LEADERS FREE complex PCI

Lipiecki J et al. EuroIntervention 2018, published online May 2018

Primary safety endpoint (cardiac death/MI/ST)



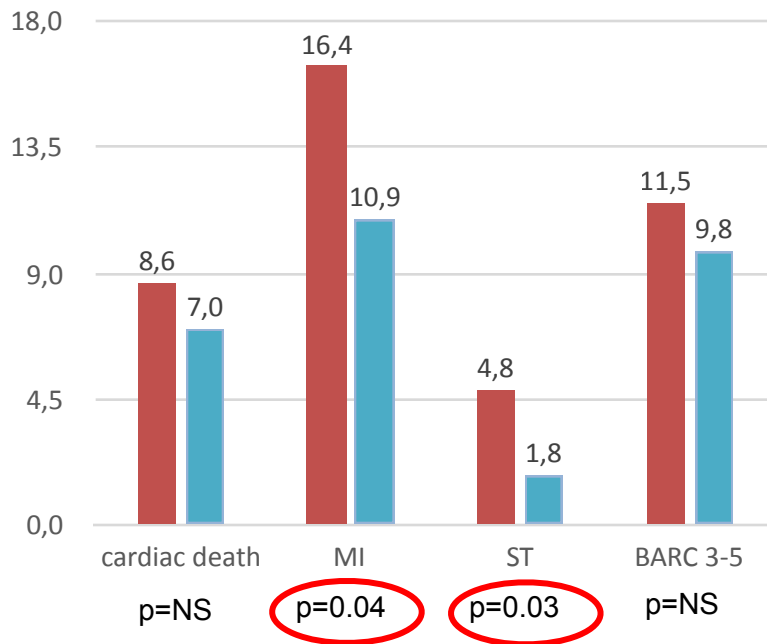
NNT
Complex 18
Non-complex 67

P for interaction = NS

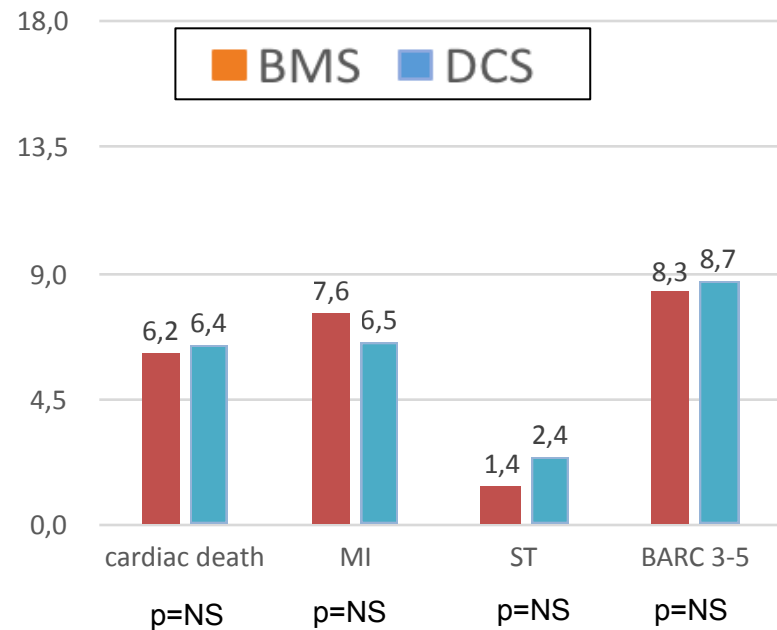
Safety & bleeding for complex PCI

Lipiecki J et al. EuroIntervention 2018, published online May 2018

Complex PCI



Non-complex PCI

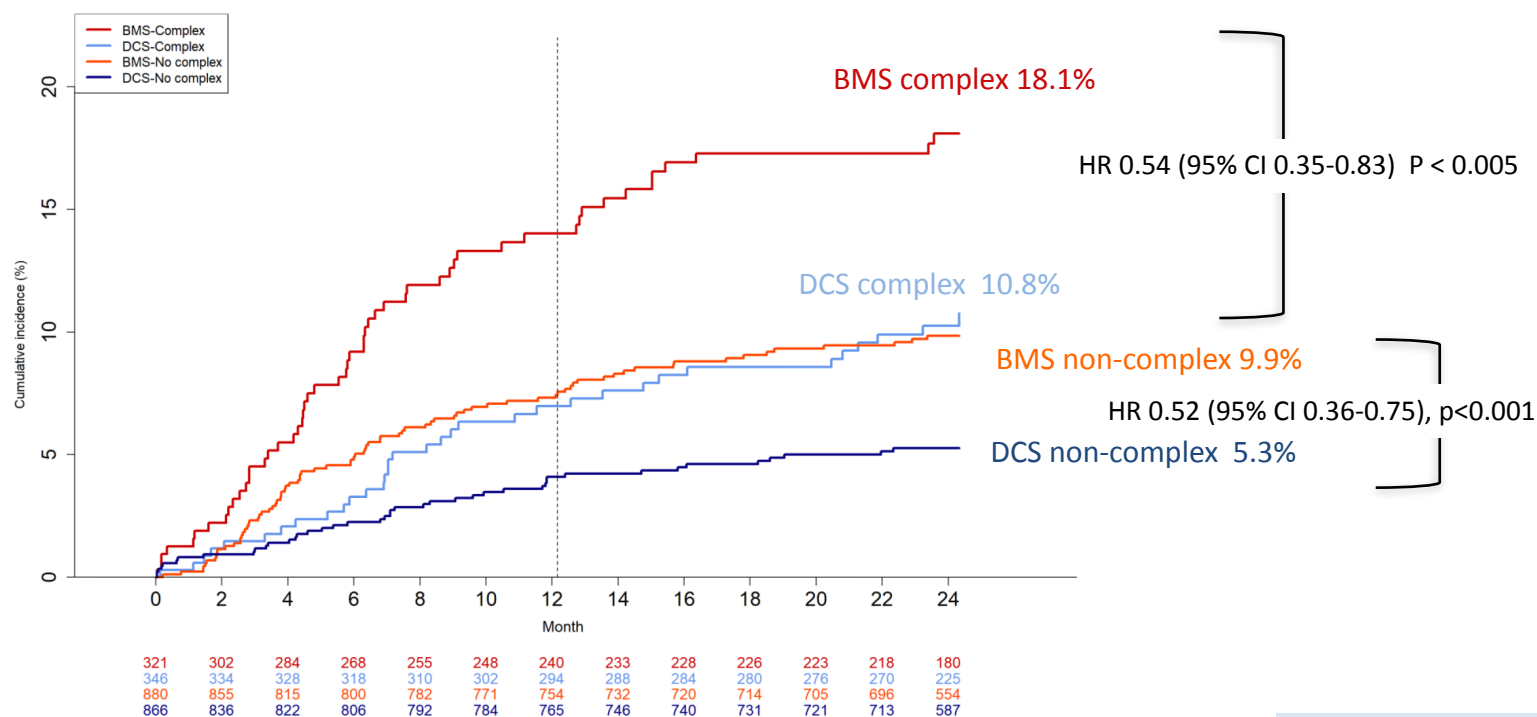


p values for interaction not significant, except for ST (0.014)

LEADERS FREE complex PCI

Lipiecki J et al. EuroIntervention 2018, published online May 2018

Primary efficacy endpoint (clinically indicated TLR)



NNT
Complex 14
Non-complex 22

P for interaction = NS



LEADERS^{FREE} Analyzed Subsets

(DCS vs. BMS – 1 Year FU)

* Urban P et al. N Engl J Med 2015
 ** Naber C et al. Eur Heart J 2016
 +++ Richardt G Euro PCR 2017 § Iniguez, Euro-PCR 2017
 §§ Lipiecki EuroIntervention 2018
 ++ Carrié D. JACC interv 2017
 + Morice M-C Intern. J Cardiol 2017

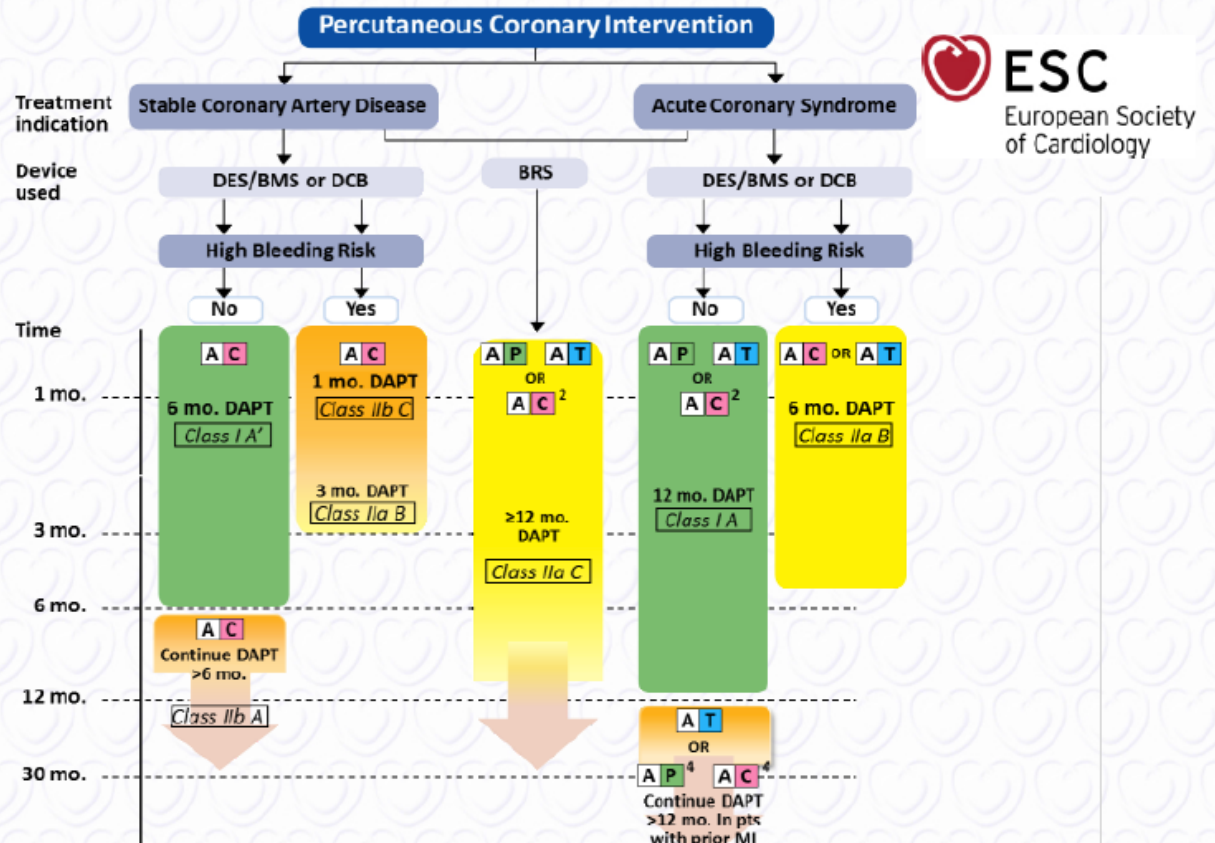
	n	Superior efficacy*	Superior safety* Composite EP)	BARC 3–5 Bleeding (DCS+BMS)
All *	2466	✓	✓	7.2%
ACS **	659	✓	✓	9.1%
Elderly (>75) +	1575	✓	✓	7.7%
Radial access§	1454	✓	✓	5.0%
Complex PCI§§	667	✓	✓	10.6%
Oral anticoagulants ++	879	✓	–	8.8%
Diabetics +++	805	✓	–	8.3%

*p <0.05 or less

2017 ESC Focused Update on DAPT in Coronary Artery Disease

(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Algorithm for dual antiplatelet therapy (DAPT) in patients treated with percutaneous coronary intervention



²:1-month DAPT after implantation of zotarolimus-eluting Endeavour sprint stent or drug coated Biofreedom stent reduced risks of reintervention, myocardial infarction and inconsistently of stent thrombosis compared to bare-metal stent under similar DAPT duration. It is unclear if this evidence applies to other contemporary DES.

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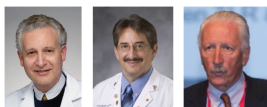
“New SAPT”

	GLOBAL LEADERS	TWILIGHT	LEADERS FREE
Anticoagulants	✗	✗	✓
Cancer		✗	✓
Recent bleed/diathesis	✗		✓
Major surgery soon	✗	✗	✓
AMI presentation		✗	not excluded
Severe liver disease	✗	✗	✓
Thrombopenia		✗	✓
Recent CVA	✗	✗	✓
Any ICH	✗	✗	✓
Use of CYP3a4 inhibitor	✗	✗	not excluded

Exclusion (✗) vs. inclusion (✓) criteria

LEADERS FREE II

LEADERS FREE II



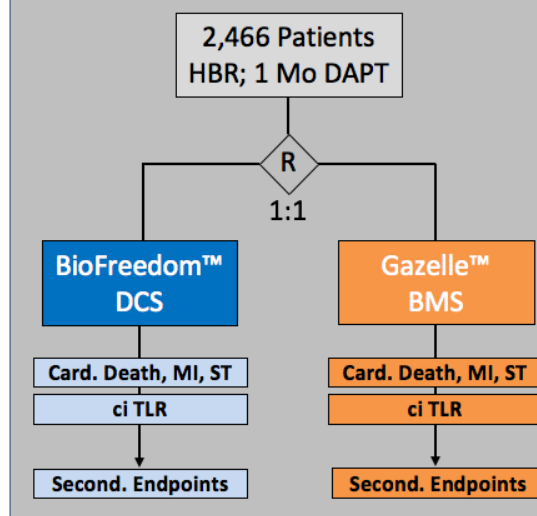
- Chairman: Dr. Marty Leon, CRF, NY
- PI: Dr. Mitch Krucoff, Duke, Durham, NC
- EU co-PI: Dr. Philip Urban, Geneva, Switzerland

- Statistics: Stuart Pocock, School of Hygiene, London
- Project Management: Corie Diaz, Syntactx, NY
- Monitoring, CEC, [Angio Corelab](#): CERC, Paris, Fr
- Data Management: Duke University, Durham, NC
- DSMB, Statistics: Cardiovascular Research Foundation, NY
- Sponsor: Biosensors Research, USA



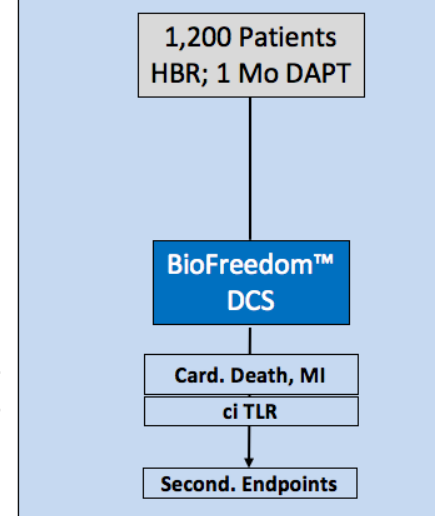
US Pivotal Trial

Leaders Free Trial

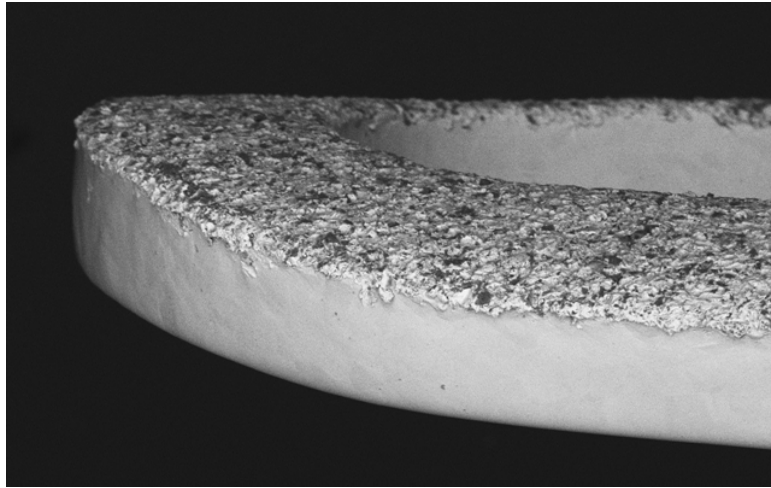


Non-
inferiority +
Superiority
comparison
↔
(Propensity
Score
Method)

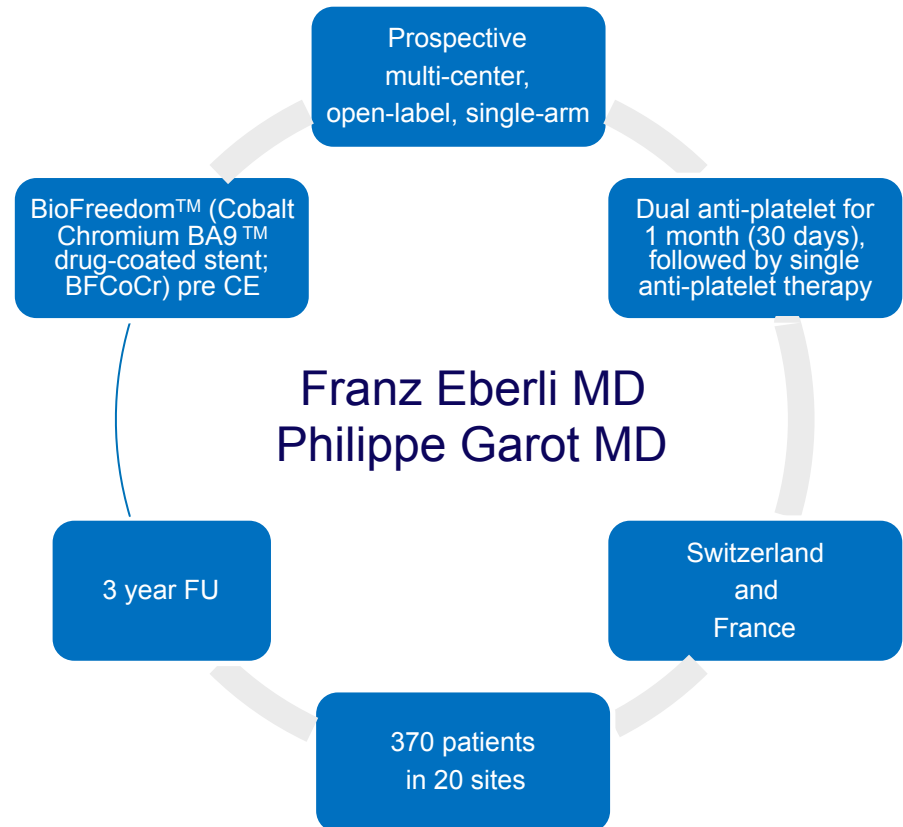
Leaders Free II Trial (US Pivotal)



LEADERS FREE III



CoCr thin struts (84-88 μm)



Trial	stent	type	limus kinetics	patients	experimental arm DAPT	control arm	Status March 2018
LEADERSFREE II	SS BioFreedom	polymer-free	fast	1200 HBR	1 month	BMS arm of LEADERS FREE	follow-up (TCT 2018?)
LEADERS FREE III	CoCr BioFreedom	Polymer-free	fast	370 HBR	1 month	DCS arm of LEADERS FREE	enrolling

Conclusions for spring 2018

- ✓ The LEADERS FREE trial has shown that the use of a BA9-DCS is both significantly safer and more effective than a control BMS in HBR patients treated with a one-month only DAPT course, both at 1 year (primary endpoint) and after 2 years follow-up
- ✓ No subgroup was identified for which use of a BMS was superior to a DCS
- ✓ >30 years after coronary stenting was introduced, and >10 years since “all comers” appeared, “HBR” is a novel concept, and the interventional community is now learning to integrate it into daily practice