Ultra-short DAPT: Are All Stents Equal?

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Korea University Anam Hospital

I have nothing to disclose !

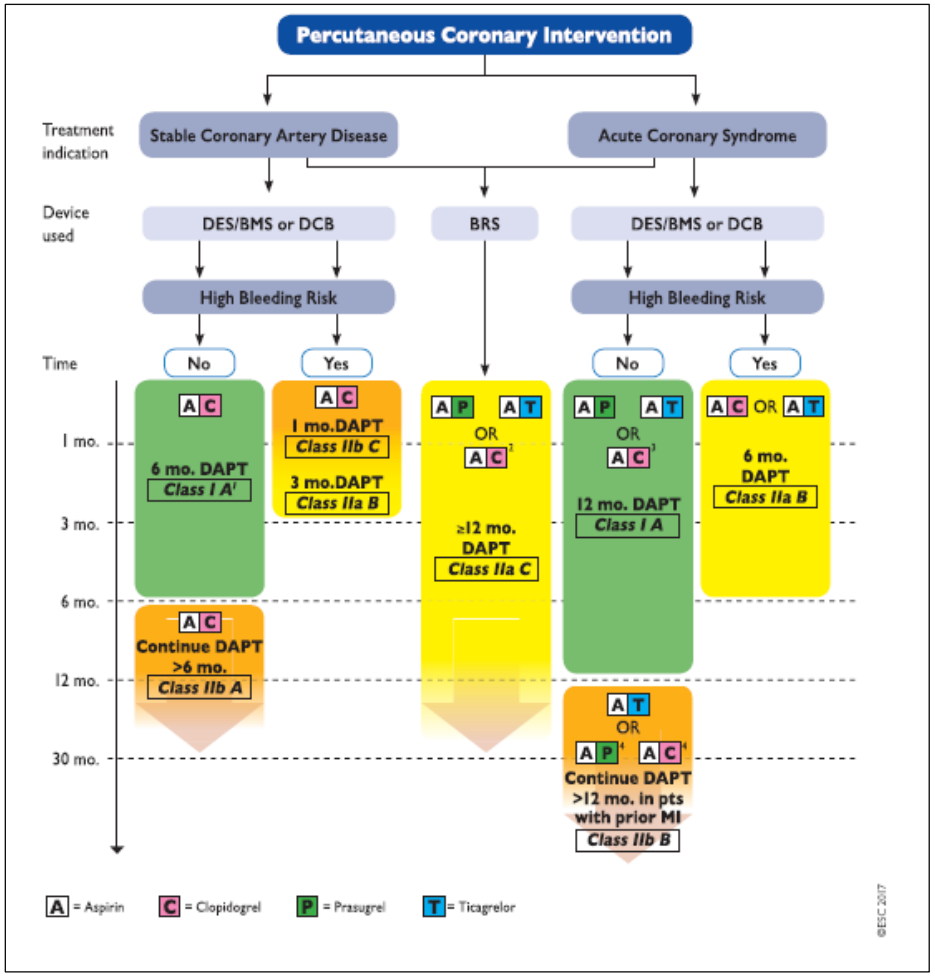
Current DAPT Guideline

ESC European Society of Cardiology
European Heart Journal (2018) 39, 213–254
doi:10.1093/eurheartj/ehx419
ESC GUIDELINES

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Marco Valgimigli* (Chairperson) (Switzerland), Héctor Bueno (Spain), Robert A. Byrne (Germany), Jean-Philippe Collet (France), Francesco Costa (Italy), Anders Jeppsson[1] (Sweden), Peter Jüni (Canada), Adnan Kastrati (Germany), Philippe Kolh (Belgium), Laura Mauri (USA), Gilles Montalescot (France), Franz-Josef Neumann (Germany), Mate Petricevic[1] (Croatia), Marco Roffi (Switzerland), Philippe Gabriel Steg (France), Stephan Windecker (Switzerland), and Jose Luis Zamorano (Spain)



- The level of evidence for shortening DAPT regimens in the current practice guidelines is weak.
- However, many companies are trying to shortened DAPT.

- FDA requires a design rationale that serves as a logic why a shortened DAPT regimen would be safe.
- **Let's first review the design elements of the BioFreedom™ stent under the specific aspect of safety for an abbreviated <u>1-month DAPT regimen</u>.**

Polymers May Cause Localized Hypersensitivity

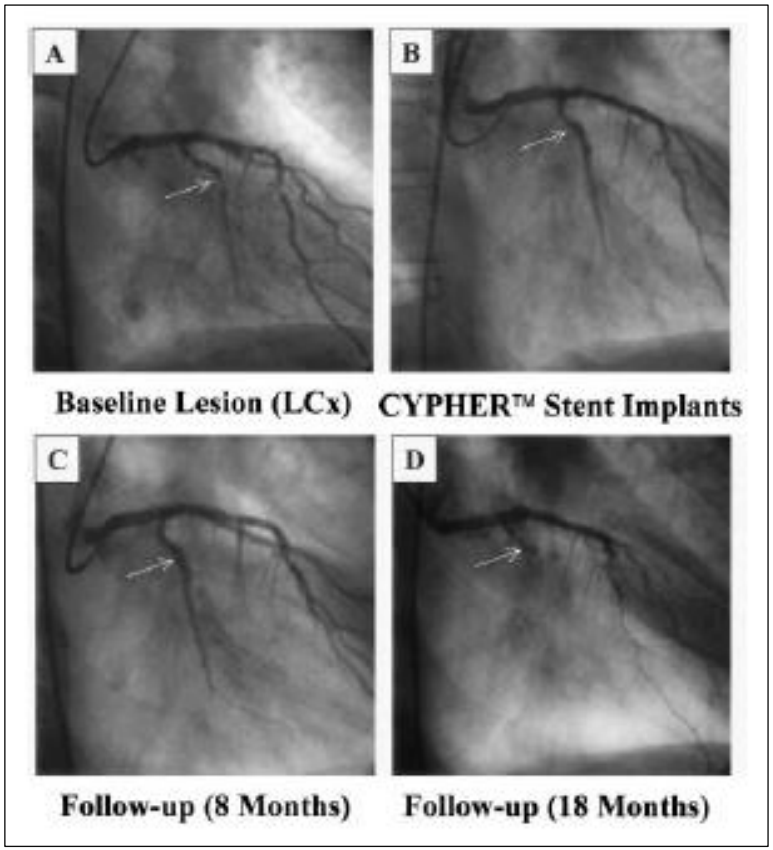
Clinical Investigation and Reports

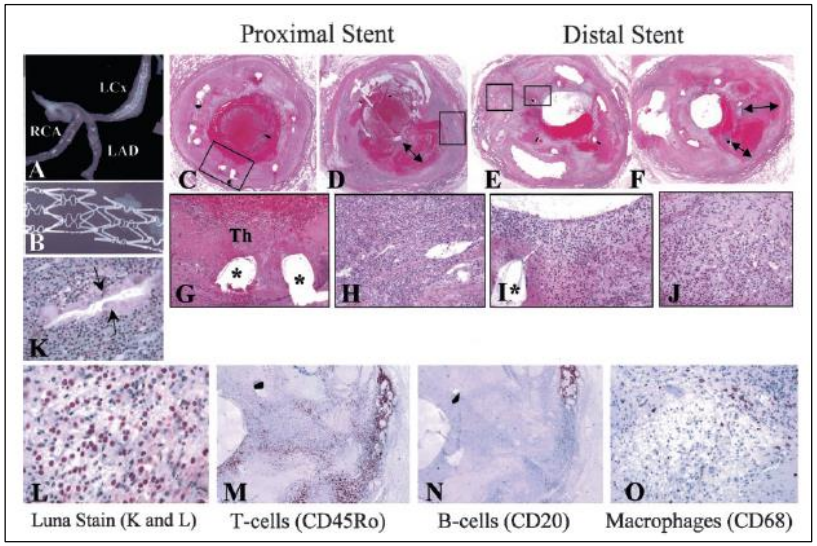
Localized Hypersensitivity and Late Coronary Thrombosis Secondary to a Sirolimus-Eluting Stent

Should We Be Cautious?

Renu Virmani, MD; Giulio Guagliumi, MD; Andrew Farb, MD; Giuseppe Musumeci, MD; Niccolo Grieco, MD; Teresio Motta, MD; Laurian Mihalcsik, MD; Maurizio Tespili, MD; Orazio Valsecchi, MD; Frank D. Kolodgie, PhD

Circulation. 2004; 109:701-705





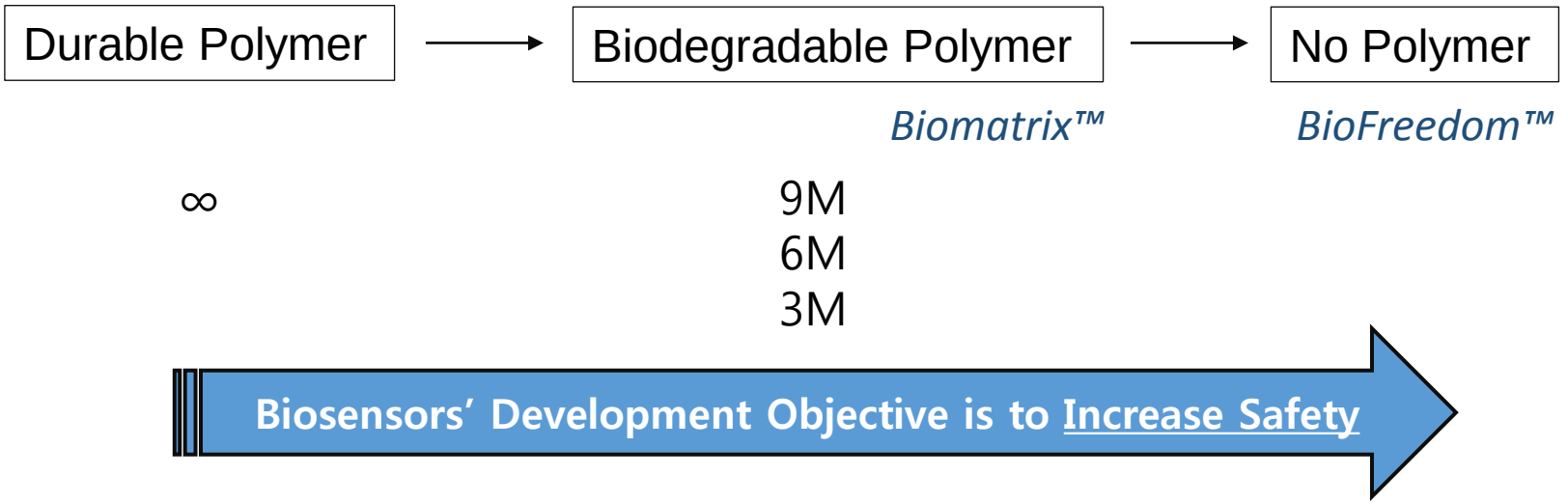
Discussion

This is the first case of a localized hypersensitivity vasculitis in response to a Cypher coronary stent resulting in an acute myocardial infarction secondary to late in-stent thrombosis at 18 months. The hypersensitivity reaction could be caused by the metallic stent, polymer, or sirolimus. Available pathological evidence, however, supports the hypothesis that hypersensitivity to the polymer is the most likely mechanism.

- First pathology report on a localized hyper-sensitivity vasculitis after Cypher™ stent implantation.
- Most likely caused by hypersensitivity to the methyl-acrylate polymer

Is the Polymer Needed ?

Presence of the polymer may require protection through DAPT, at least early after implantation.



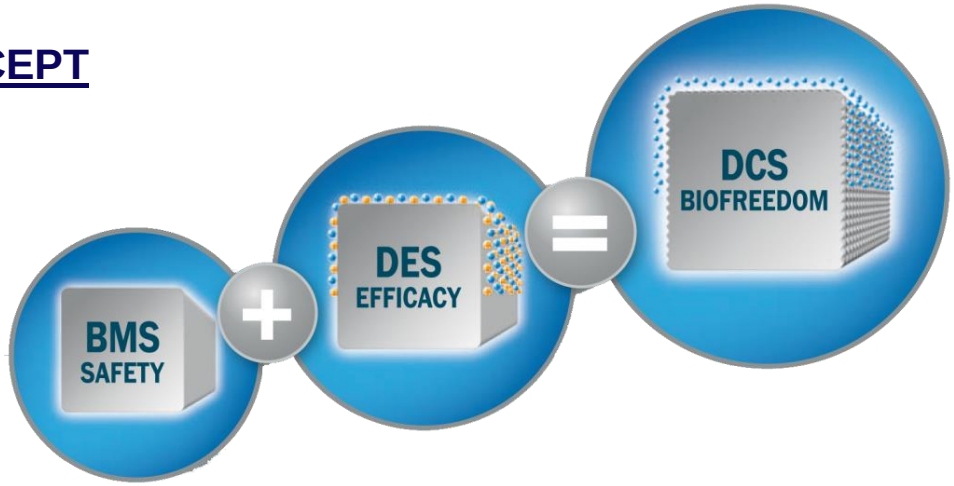
- Due to the time course of the arterial response to injury, exposure to the vessel wall to an anti-proliferative drug is needed for a period of approx. 90 days (3M) to prevent neointimal proliferation.
- The purpose of a polymer is to modulate the drug release to match this 90 day requirement.
- How can a polymer-free stent be effective in restenosis prevention?

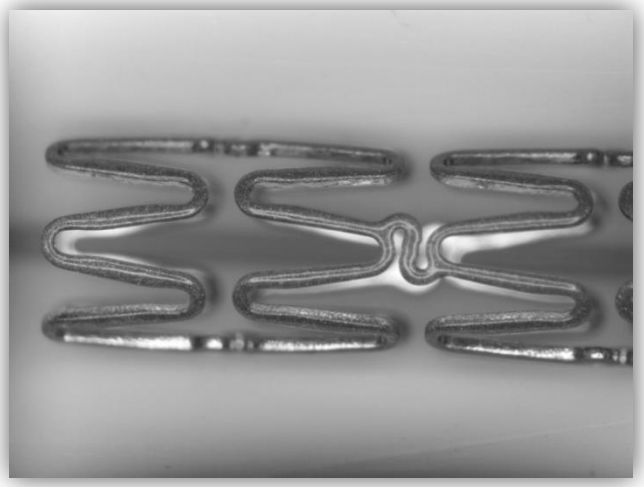
Critical Design Elements of BioFreedom™

- No Polymer
- Selectively modified abluminal surface
- **Hyper-lipophilic Drug (BA-9)**

The BioFreedom™ Drug-Coated Stent

CONCEPT

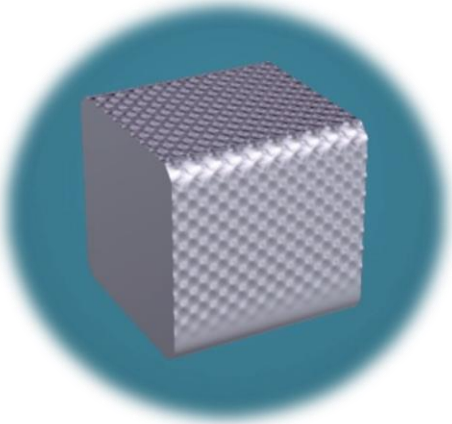




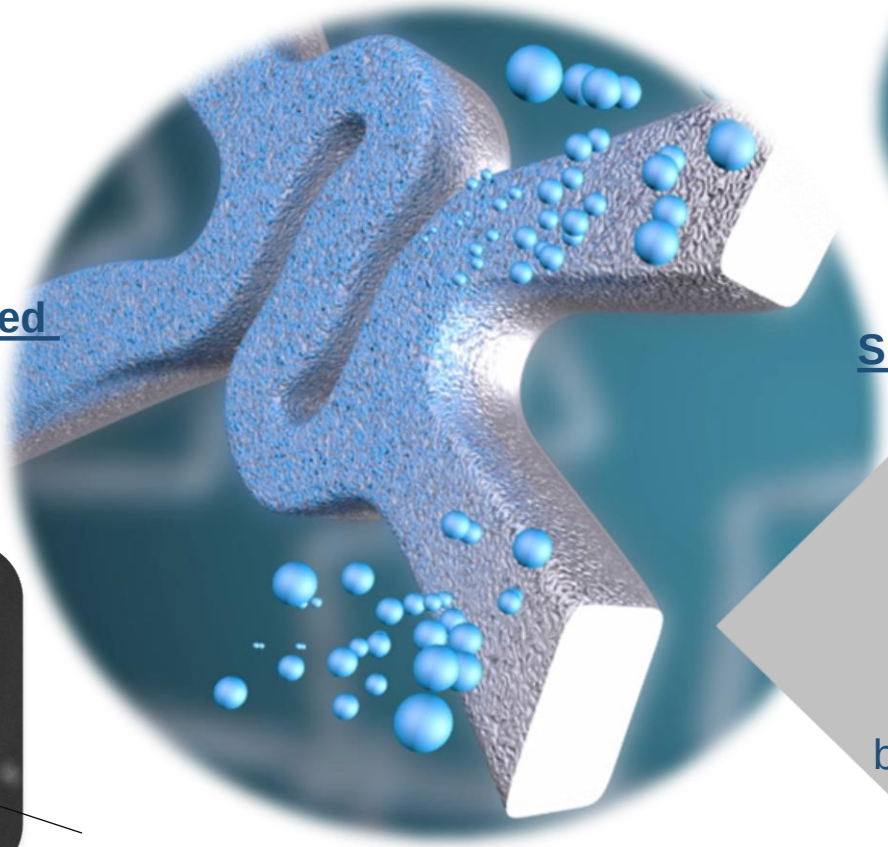
Proprietary Technology

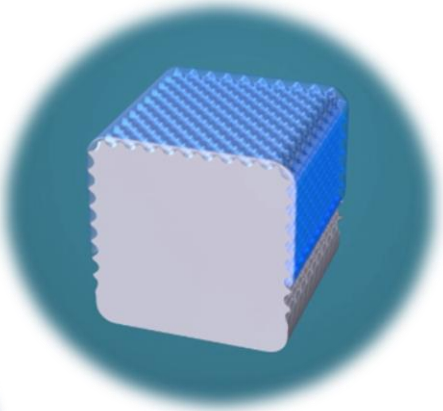
- Polymer-free drug delivery to lesion site
- Process of making selectively micro-structured surface on the stent abluminal side

Selectively Modified Abluminal Surface



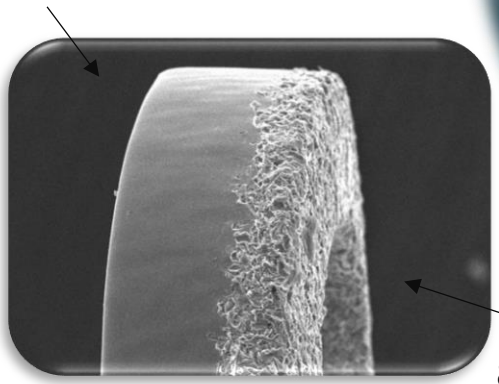
Selectively Microstructured Abluminal Surface





Smooth Luminal Surface

luminal

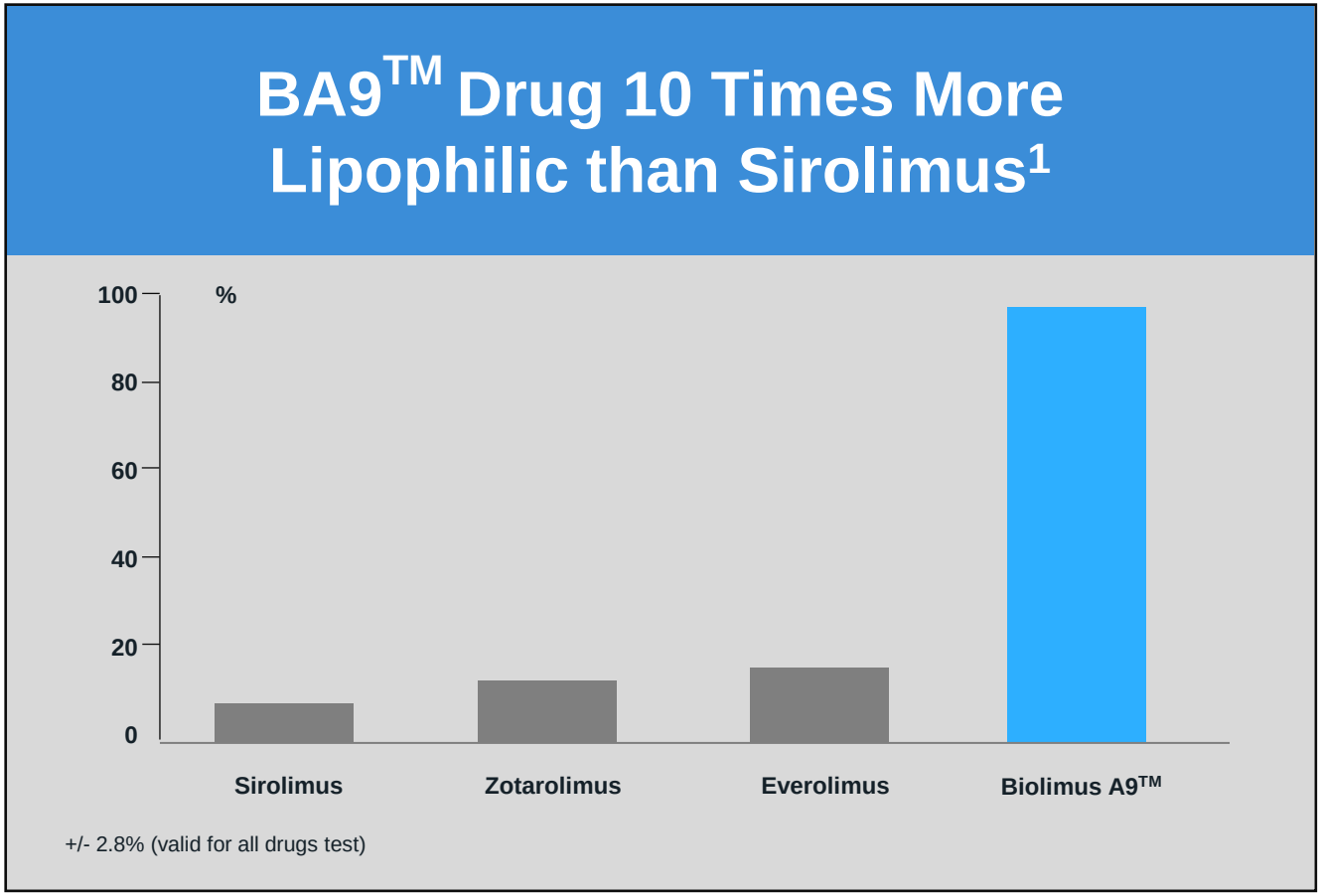


abluminal

After about 28 days, when approx. 98% of the drug has been transferred to the vessel wall, the BioFreedom becomes a bare metal stent.[1]

1. In vivo data shows that approximately 2% of BA9 remains on the stent after 28 days. Data on file at Biosensors International

BA-9 is a Hyper-Lipophilic Anti-Proliferative Drug

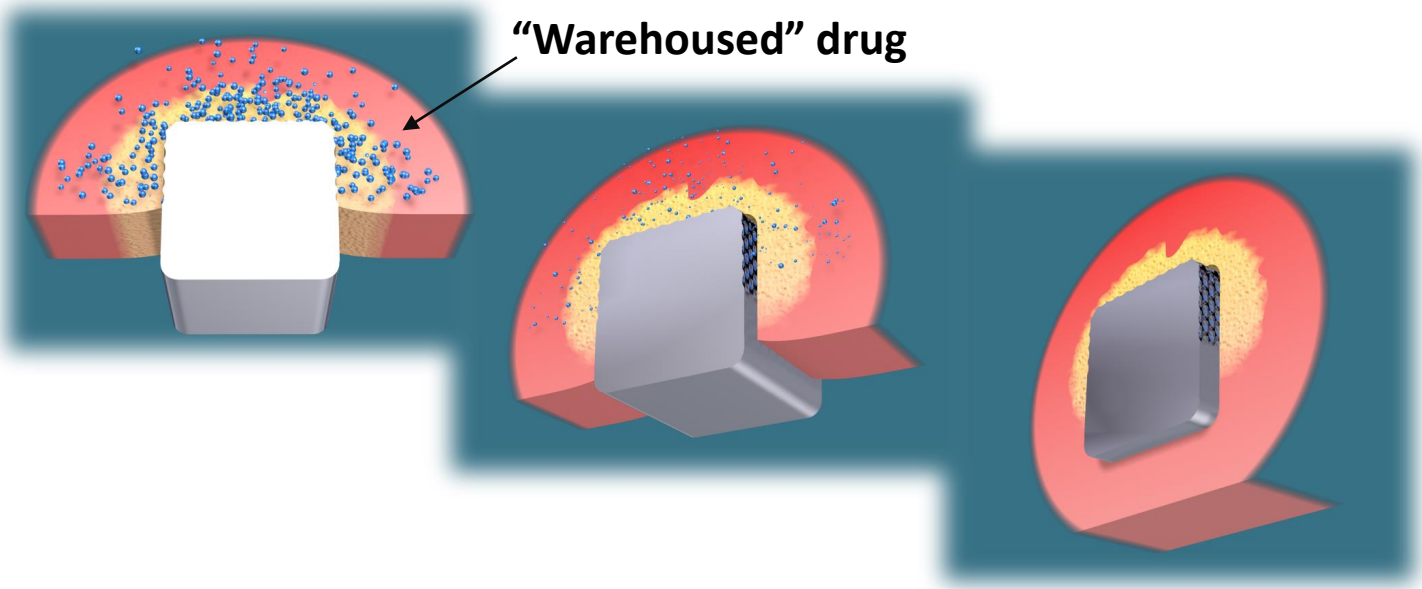


- The high lipophilicity of the BA-9 drug allows for sustained "warehousing" in the vessel wall after drug transfer, long enough to cover the initial 90-day period.
- The polymer-free design would likely not result in a restenosis with a lipophilic BA-9.

1. Data on file at Biosensors Intl; 2. Tada et al., Circ Cardiovasc Interv 2010;3;174-183

The Concept of Local Tissue Drug "Warehousing"

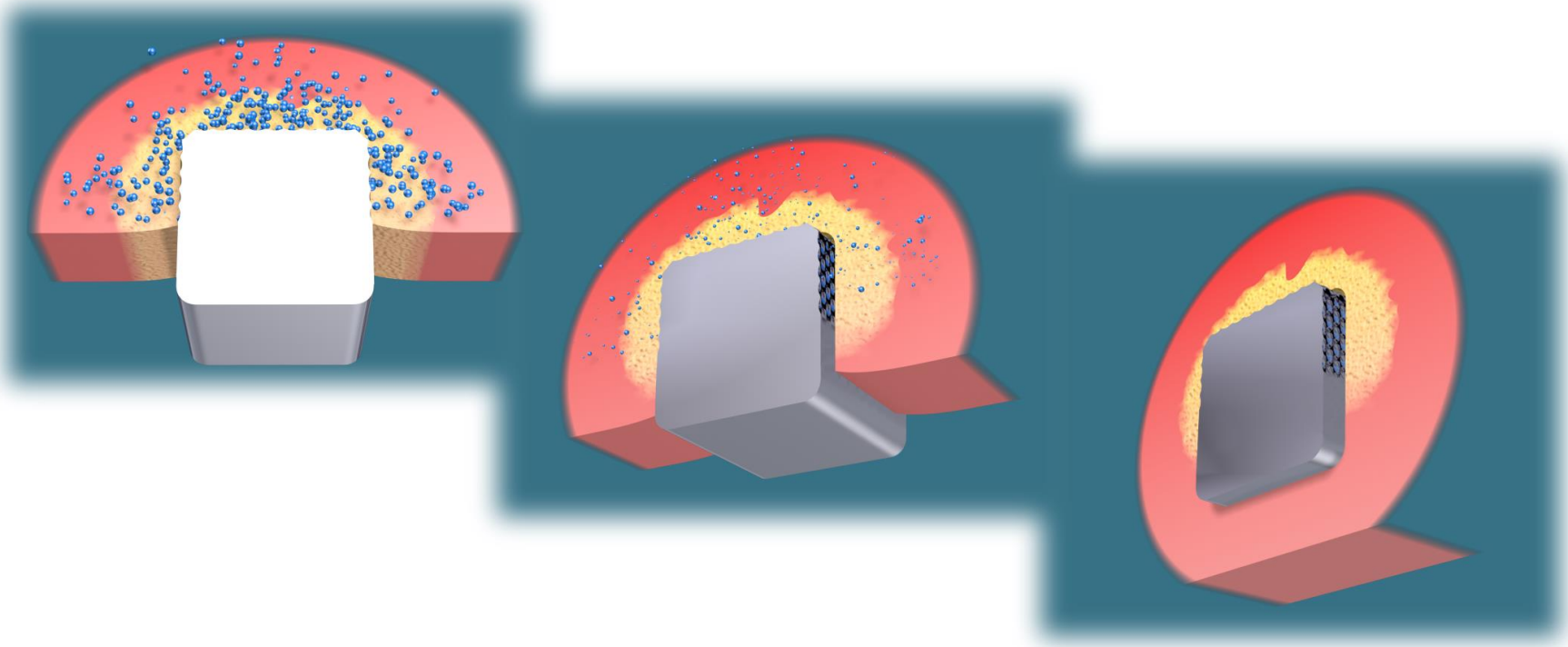
- Instead of being slowly released from a polymer, the drug is transferred fast (<28 days) and locally stored in the adjacent vessel wall tissue.



Polymers 2014, 6, 2309-2331; doi:10.3390/polym6092309

Purpose of Selectively Micro-structured Surface

- Increase surface area to physically contain drug
- Minimize drug loss during navigation to target lesion site
- Target drug delivery towards vessel wall



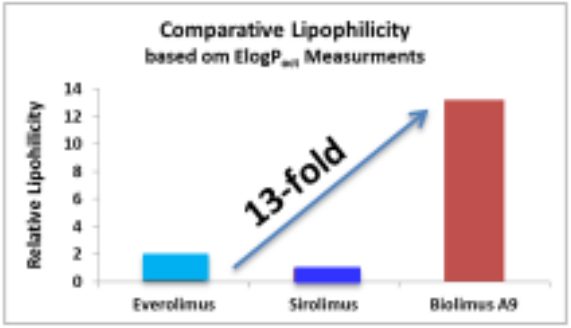
Polymers 2014, 6, 2309-2331; doi:10.3390/polym6092309

Polymer-free Design: BA-9 vs. Sirolimus

2018 euro PCR

Hypothesis: drug lipophilicity dictates PF DCS release & tissue retention

- **Biolimus A9 (BA9)** is a highly lipophilic Sirolimus analog specifically designed for local-drug delivery.



- **To control lipophilicity** we contrasted BA9 and Sirolimus PF DCS stents (Biosensors International) coated with the same drug load (225µg) via the same abluminal surface texturing and spray coating processes of BioFlex II stents.

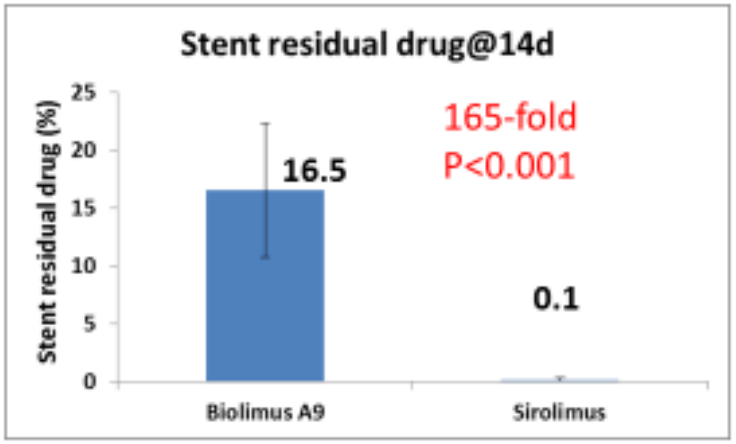
CBSET
INNOVATING TECHNOLOGY
INTEGRATING SCIENCE

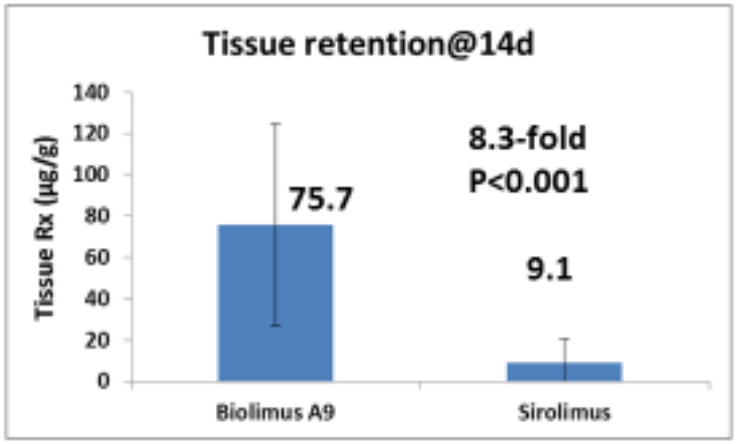
Pre-Clinical Work Verified BA-9 Retention

2018 euro PCR

Lipophilicity dictated bulk release and tissue retention in rabbit arteries

- Biolimus Vs. sirolimus PF DCS were implanted into illiofemoral arteries of **11 NWZ rabbits**.
- Drug content was quantified by LC/MS/MS in arteries and stents at sacrifice (@14d).



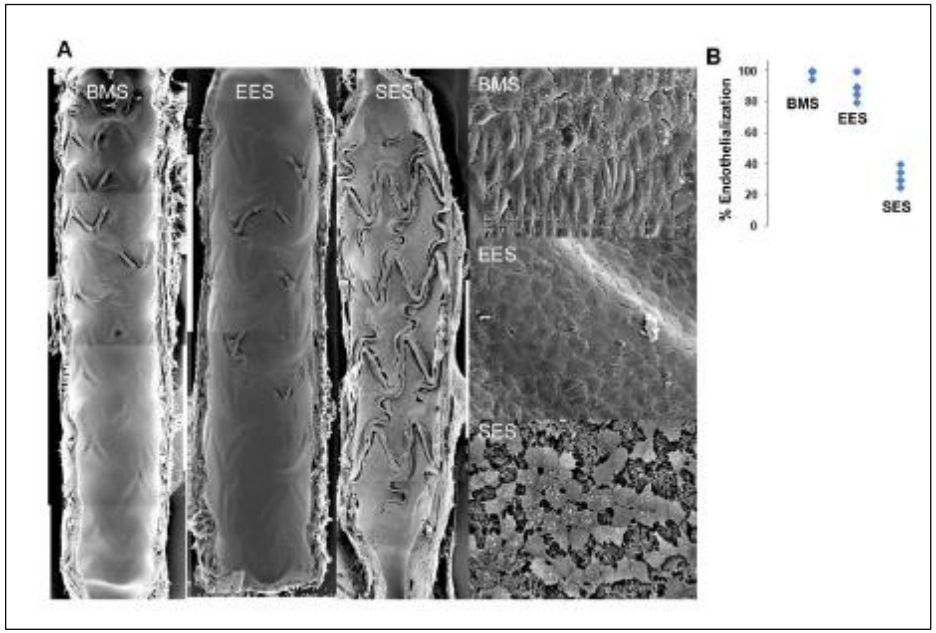


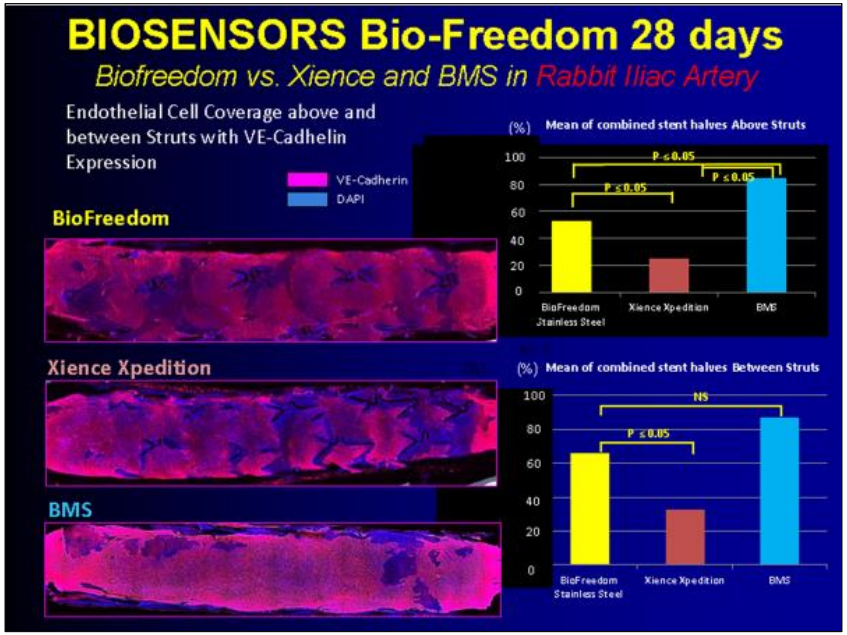
CBSET INNOVATING TECHNOLOGY INTEGRATING SCIENCE

Tzafriri et al, PCR 2017

Rabbit Iliac Model – Endothelial Coverage

Rabbit Iliac Stent Model with SEM imaging at 14 days





Circ Cardiovasc Interv. 2014; 7:526-532

- In the rabbit iliac model, BioFreedom stents were covered with endothelial tissue at 14 days, at a level similar to bare-metal stents.
- This finding suggests that a DAPT period of 1 month, which has been the standard for BMS, can be considered once needed for high bleeding risk patients.

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 373;21 NEJM.ORG NOVEMBER 19, 2015

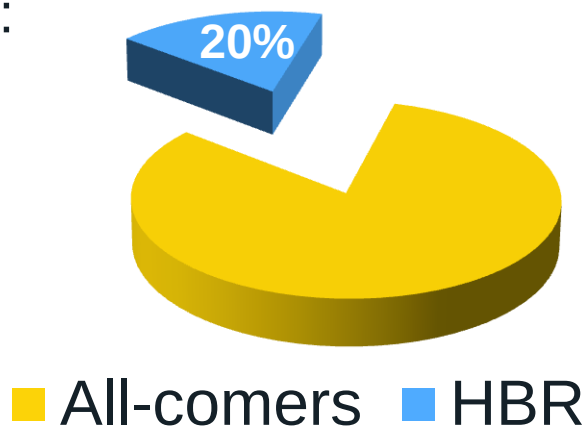
ORIGINAL ARTICLE

Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk

Philip Urban, M.D., Ian T. Meredith, M.B., B.S., Ph.D., Alexandre Abizaid, M.D., Ph.D., Stuart J. Pocock, Ph.D., Didier Carrié, M.D., Ph.D., Christoph Naber, M.D., Ph.D., Janusz Lipiecki, M.D., Ph.D., Gert Richardt, M.D., Andres Iñiguez, M.D., Ph.D., Philippe Brunel, M.D., Mariano Valdes-Chavarri, M.D., Ph.D., Philippe Garot, M.D., Suneel Talwar, M.B., B.S., M.D., Jacques Berland, M.D., Mohamed Abdellaoui, M.D., Franz Eberli, M.D., Keith Oldroyd, M.B., Ch.B., M.D., Robaayah Zambahari, M.B., B.S., M.D., John Gregson, Ph.D., Samantha Greene, B.A., Hans-Peter Stoll, M.D., and Marie-Claude Morice, M.D., for the LEADERS FREE Investigators*

High Bleeding Risk Patients (HBR)

- **<u>Mostly excluded</u> from device and APT trials**
- **Never specifically studied**
- **Current guideline recommendations**:
  - BMS → one month DAPT
  - DES → "shortened" DAPT



LEADERS FREE Trial Design

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

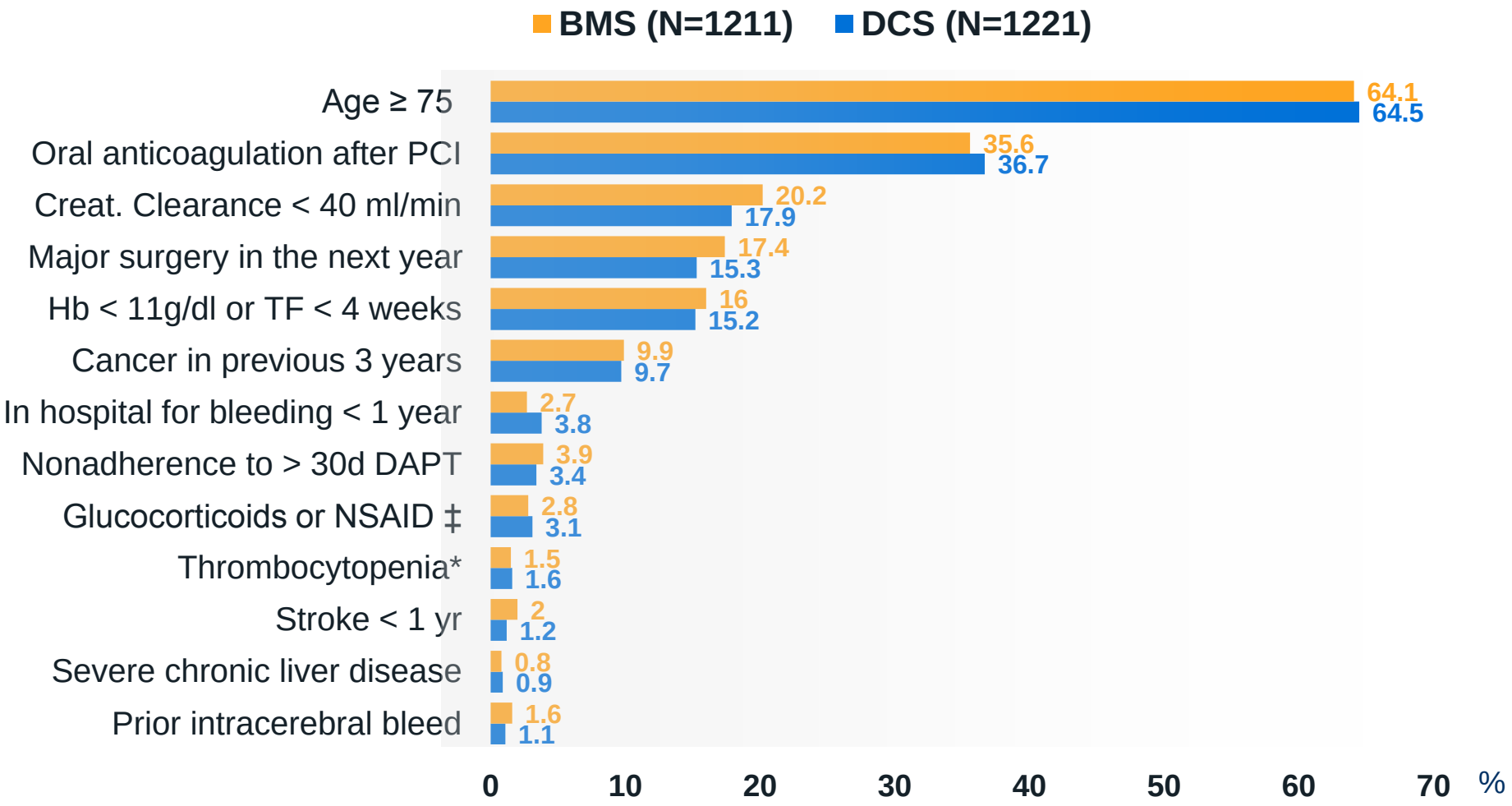
BioFreedom™ DCS **VS.** **Gazelle™ BMS**

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)

Inclusion Criteria Applied
(1.7 criteria / patient)

11697-000-EN-Rev: 01



Primary Endpoints at 1 year

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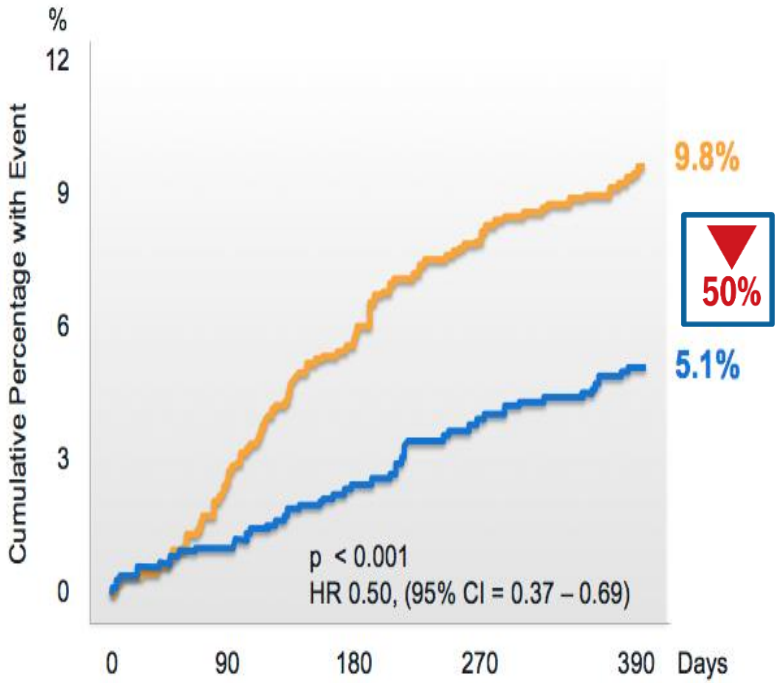
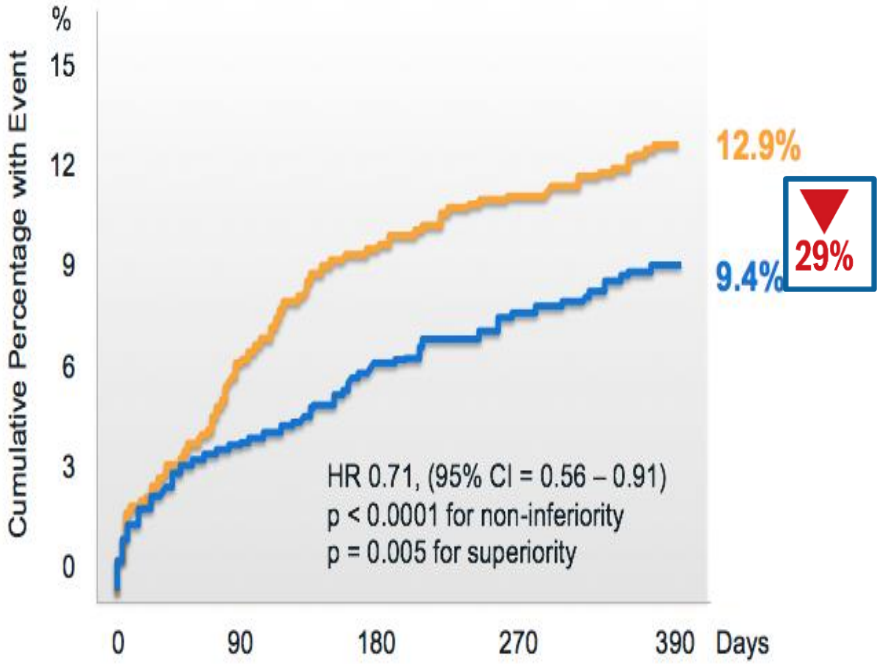
Primary Efficacy Endpoint (clinically driven-TLR)

DCS BMS



Primary Safety Endpoint (cardiac death, MI, ST)

DCS BMS



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

LEADERS FREE

Two-Year Outcomes of High Bleeding Risk Patients after Polymer-Free Drug-Coated Stents

Philip Urban, Philippe Garot, Damras Tresukosol,
Stuart J. Pocock, Ian Meredith, Alex Abizaid, Didier Carrié, Christoph Naber, Andes Iñiguez, Suneel Talwar,
Ian B.A. Menown, Evald H. Christensen, Samuel Copt,
John Gregson, Hans-Peter Stoll,Samantha Greene,
and Marie-Claude Morice for the LEADERS FREE Investigators

Presented by P Urban TCT 30th Oct 2016

Primary Safety Endpoint (Cardiac Death, MI, ST) at 2 years

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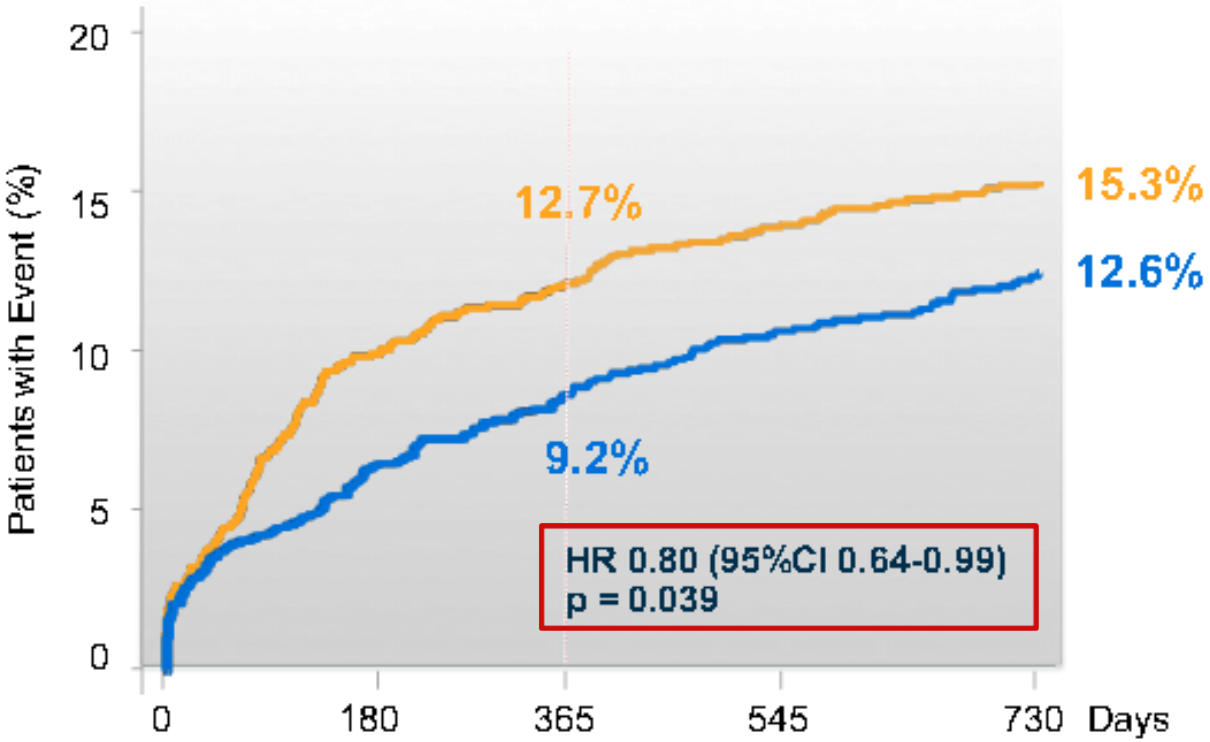

Number at Risk

DCS	1221	1104	1052	1006	620
BMS	1211	1067	1010	973	587

2 year FU was obtained at 730 days +60 days

Components of Safety Endpoint at 2 years

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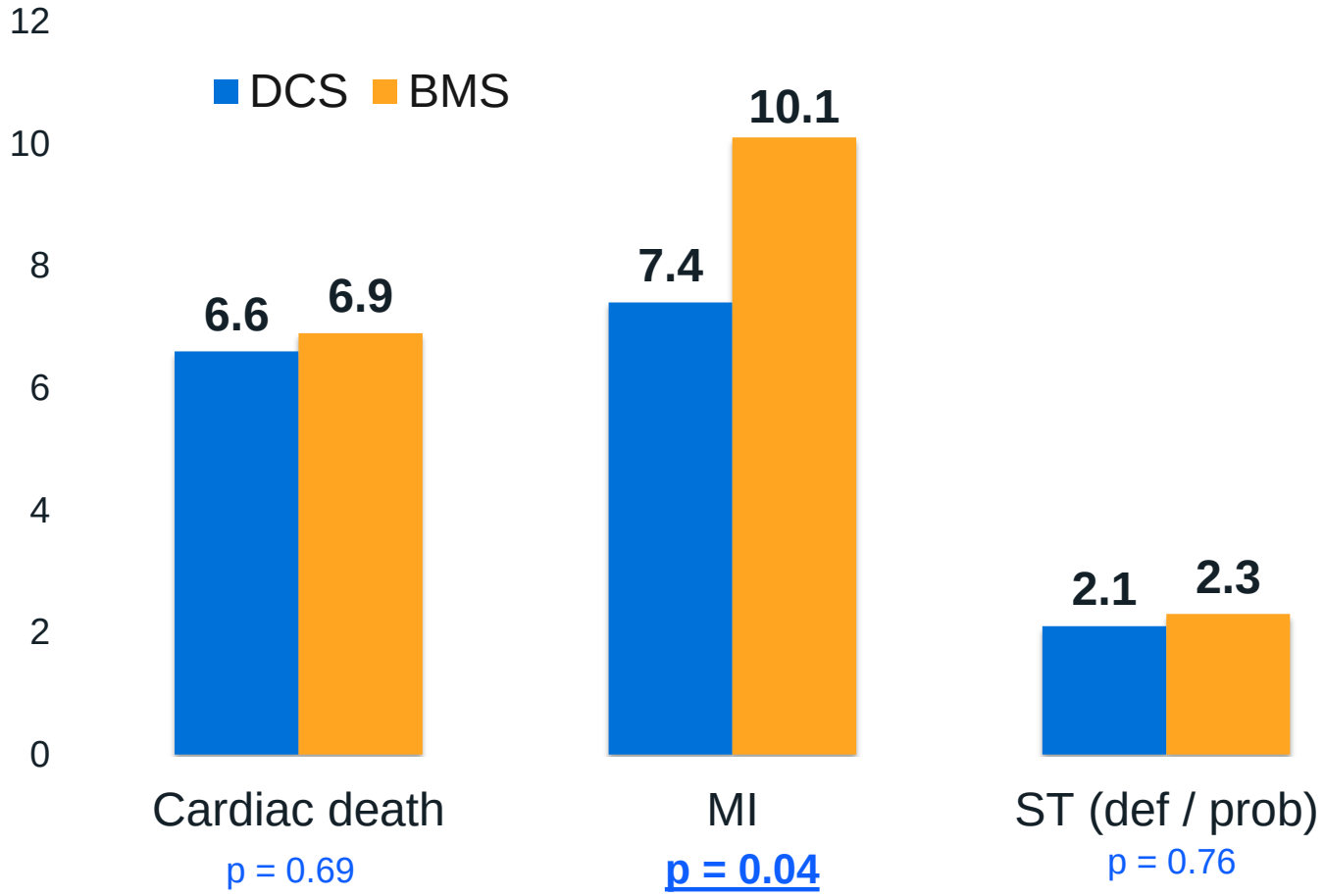
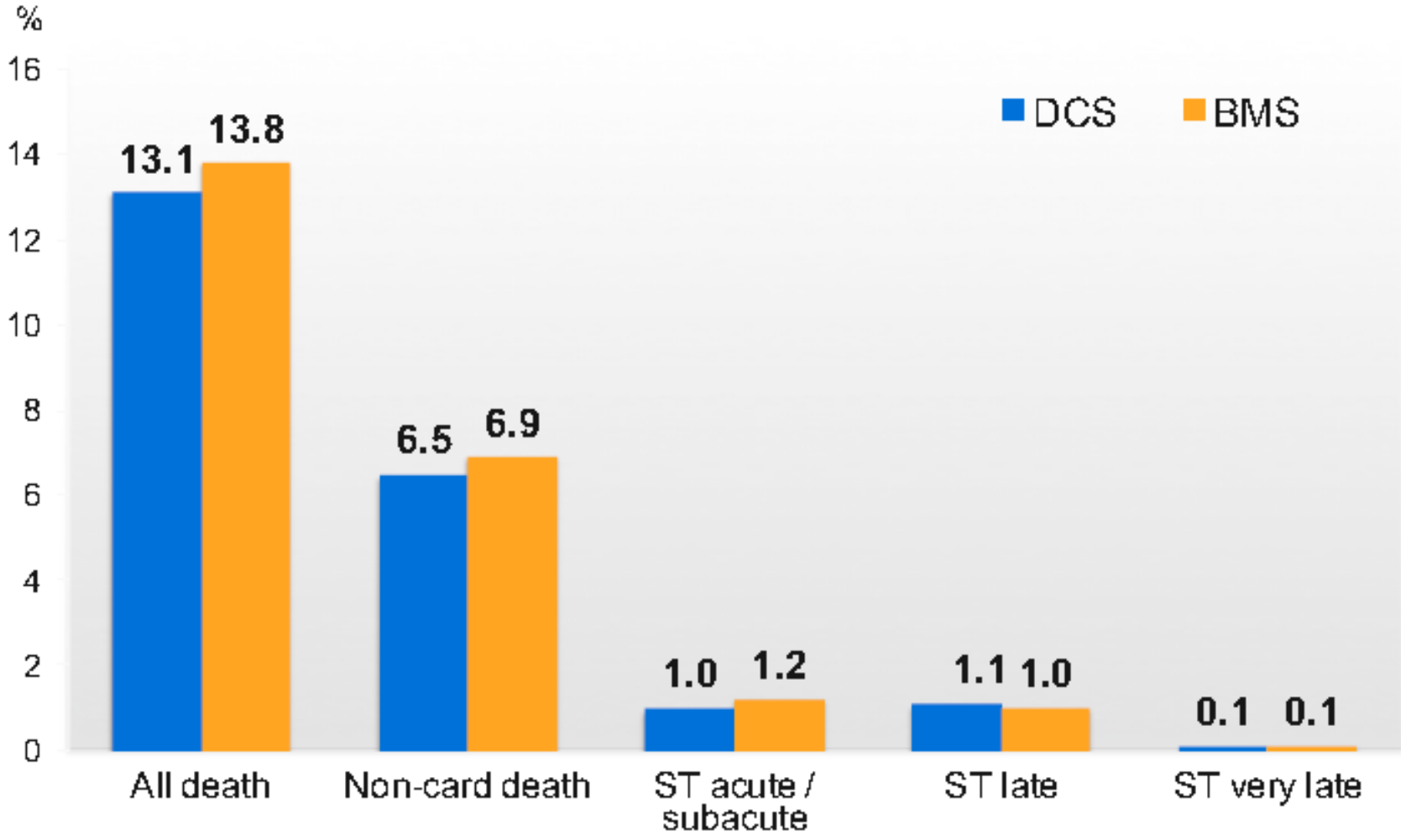


Selected Secondary Safety Endpoints at 2 years



None of these endpoints differ at p < 0.05

11697-000-EN-**Rev:** 01

Primary Efficacy Endpoint (Clinically-Driven TLR) at 2 years

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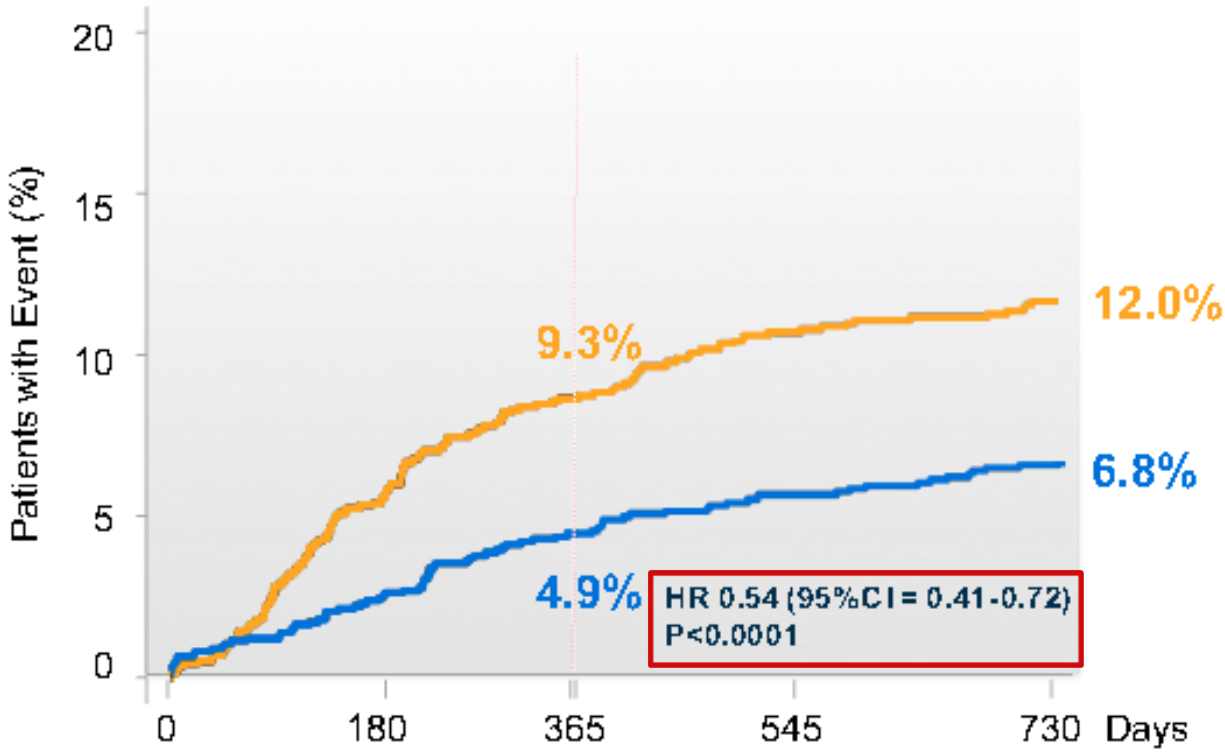


Number at Risk

DCS	1221	1129	1061	1013	626
BMS	1211	1074	999	945	561

2 year FU was obtained at 730 days +60 days

LEADERS FREE II

Pivotal Study of the Biolimus A9™ Drug-Coated Stent in High Bleeding Risk Patients: Primary Report

Presented in TCT 2018
on behalf of
Philip Urban (EU-PI), Study Leadership and the LEADERS FREE II Investigators

LEADERS FREE II Study

Pivotal Trial Supporting U.S. Device Registration Decision

***Reproducibility* of LEADERS FREE findings**

- **Safety of DCS with 30 day DAPT in HBR patients**
- **Effectiveness of DCS with 30 day DAPT in HBR patients**

***Generalizability* of LEADERS FREE findings**

- **North American patients and clinical practice**

Single arm design:

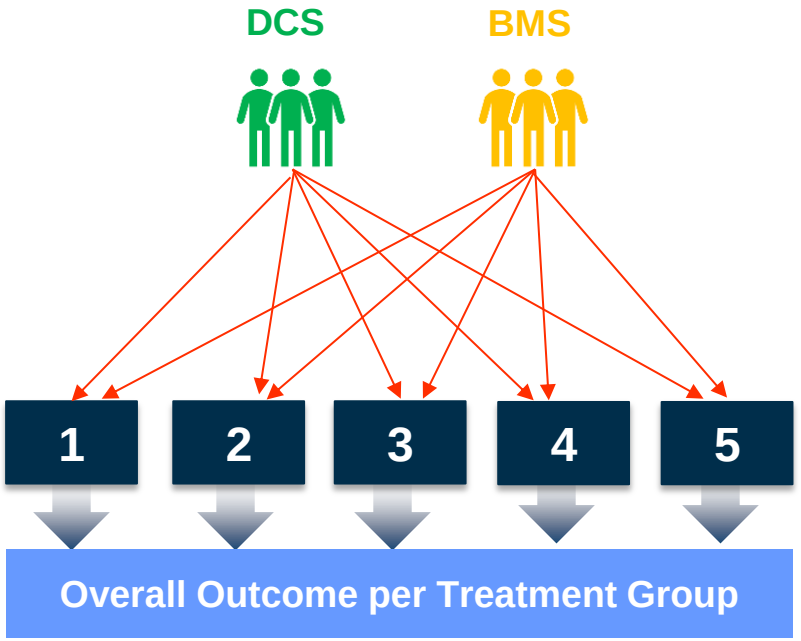
- **No equipoise for BMS randomization**

LEADERS FREE II
Statistical Analysis Plan

- ***Controls*: Leaders Free BMS patients (n=1,189)**
- ***Primary Safety Endpoint*: Composite of cardiac death and MI at 1 year** (non-inferiority then superiority)
- ***Primary Efficacy Endpoint*: Clinically-driven TLR at 1 year** (superiority)

Propensity Analysis:

- **40 baseline variable propensity profile**
- **5 strata** (quintiles)
  - Compute Primary Endpoint per treatment within quintile
  - Average treatment effect over quintiles

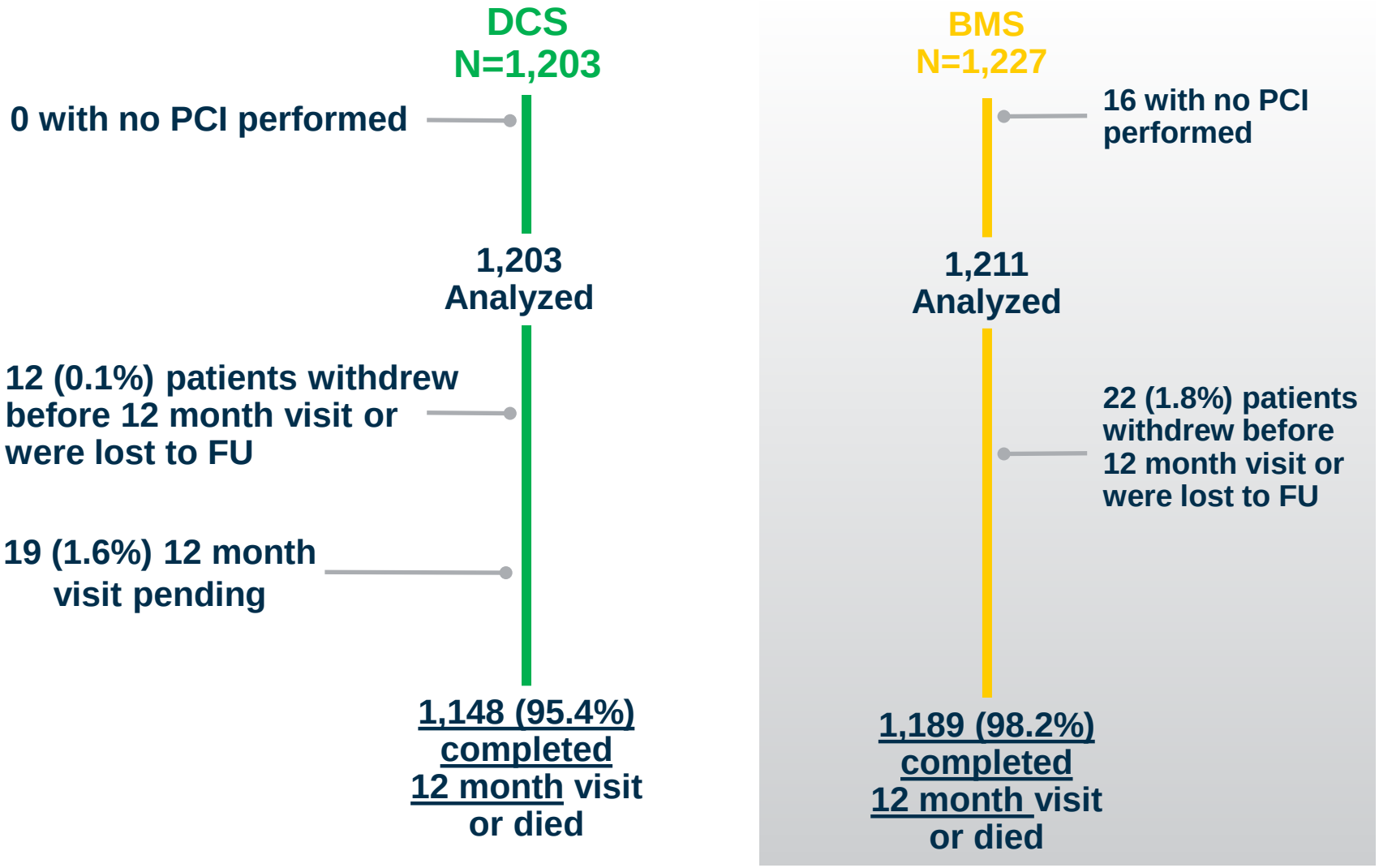


Clinical Trial Operations

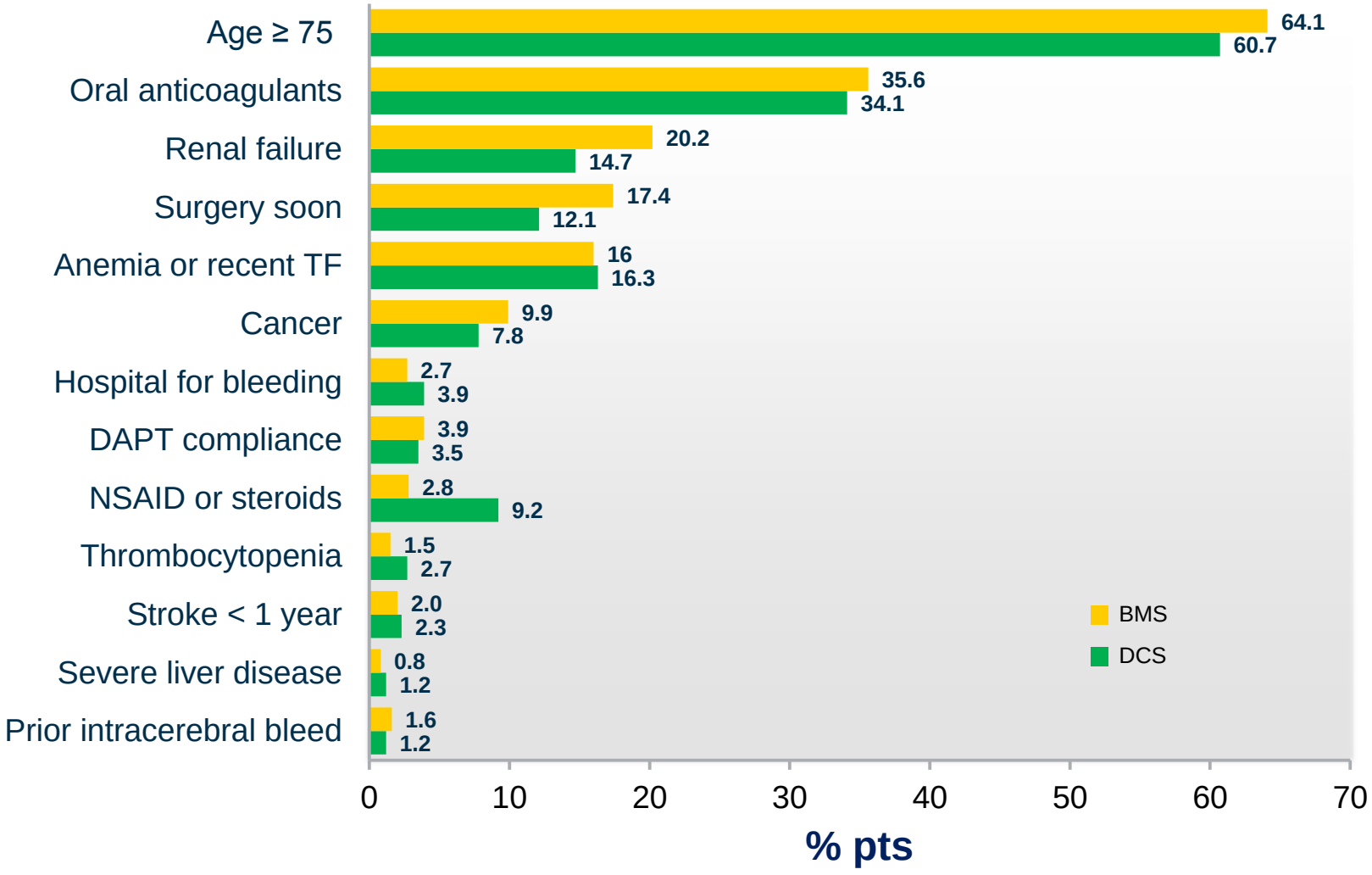
Optimizing single arm design in the absence of randomization

- **Identical inclusion / exclusion criteria**
- **Identical case report forms**
- **Identical angiographic core laboratory**
- **Identical CEC adjudication processes and committee**
- **Identical outcome endpoints**
- **Overlap of European sites**

Enrollment: LFII and LF Controls



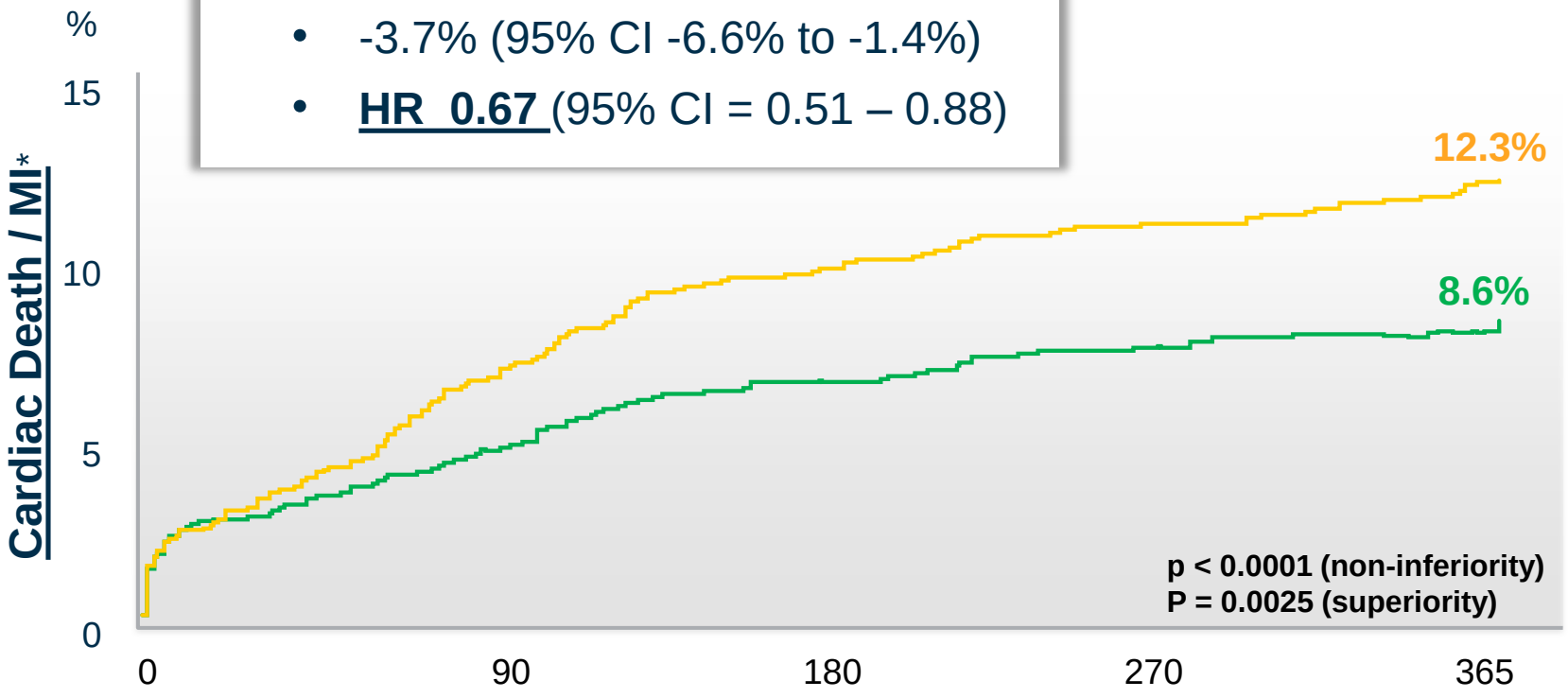
Inclusion Criteria Applied (1.74 criteria / patient)



Primary Safety Endpoint

Risk Difference:

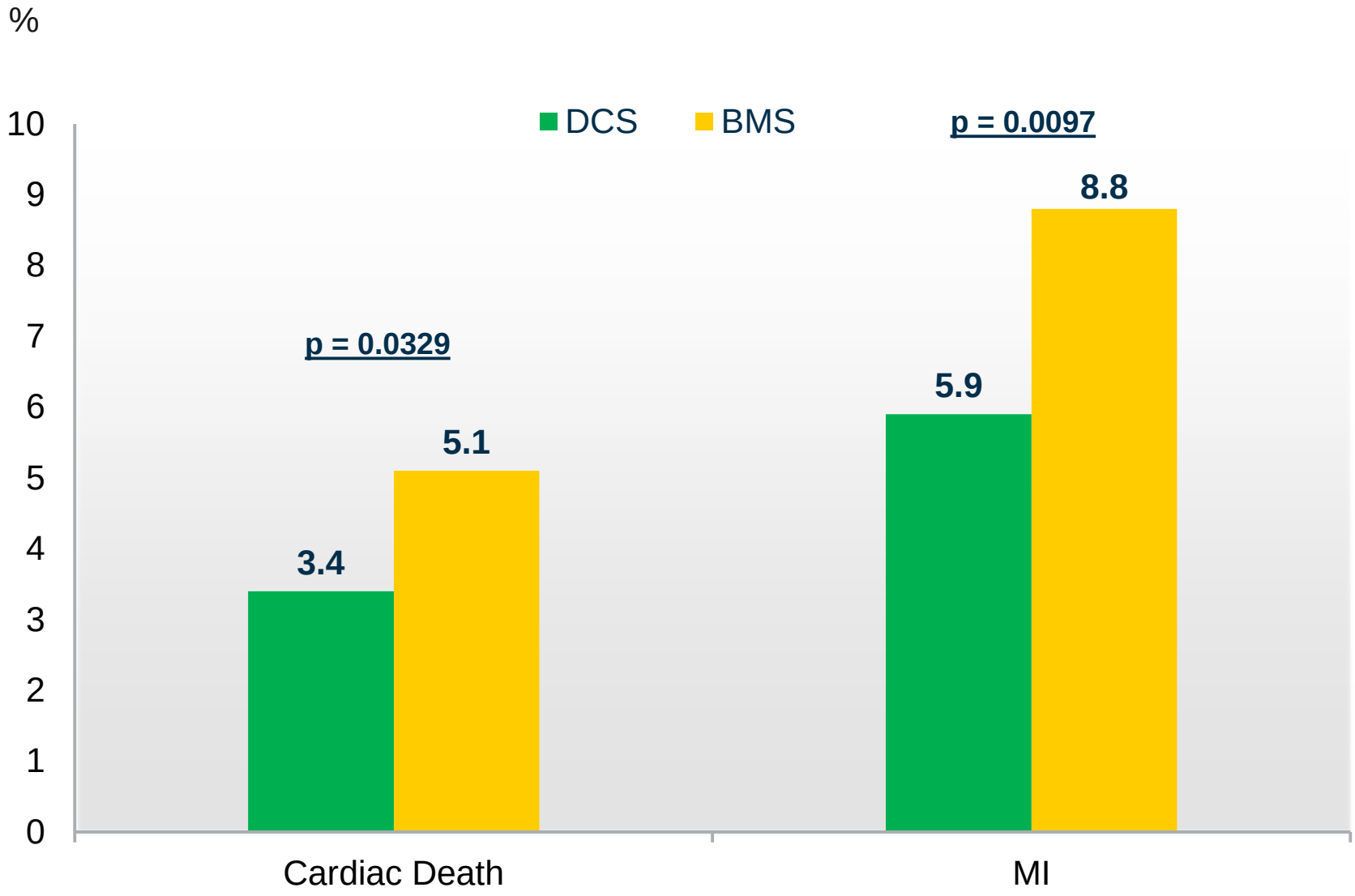
- -3.7% (95% CI -6.6% to -1.4%)
- **HR 0.67** (95% CI = 0.51 – 0.88)



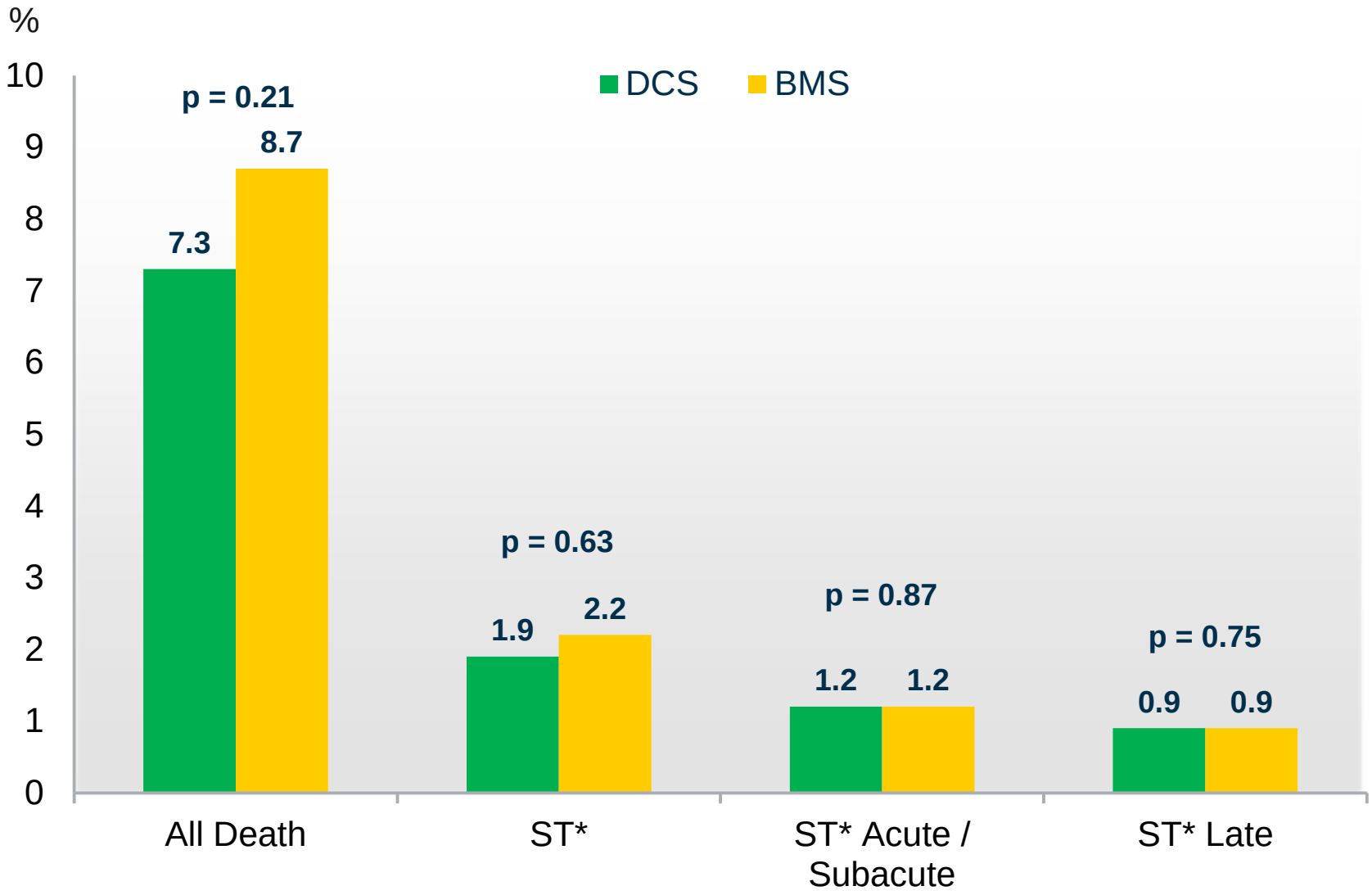
Number at Risk					
BMS	1,211	1,117	1,066	1,040	1,013
DCS	1,203	1,124	1,086	1,039	469

*3rd Universal definition of MI, Thygesen K et al Circulation 2012;126:2020 –2035.

Components of Safety Endpoint



Selected Secondary Safety Endpoints

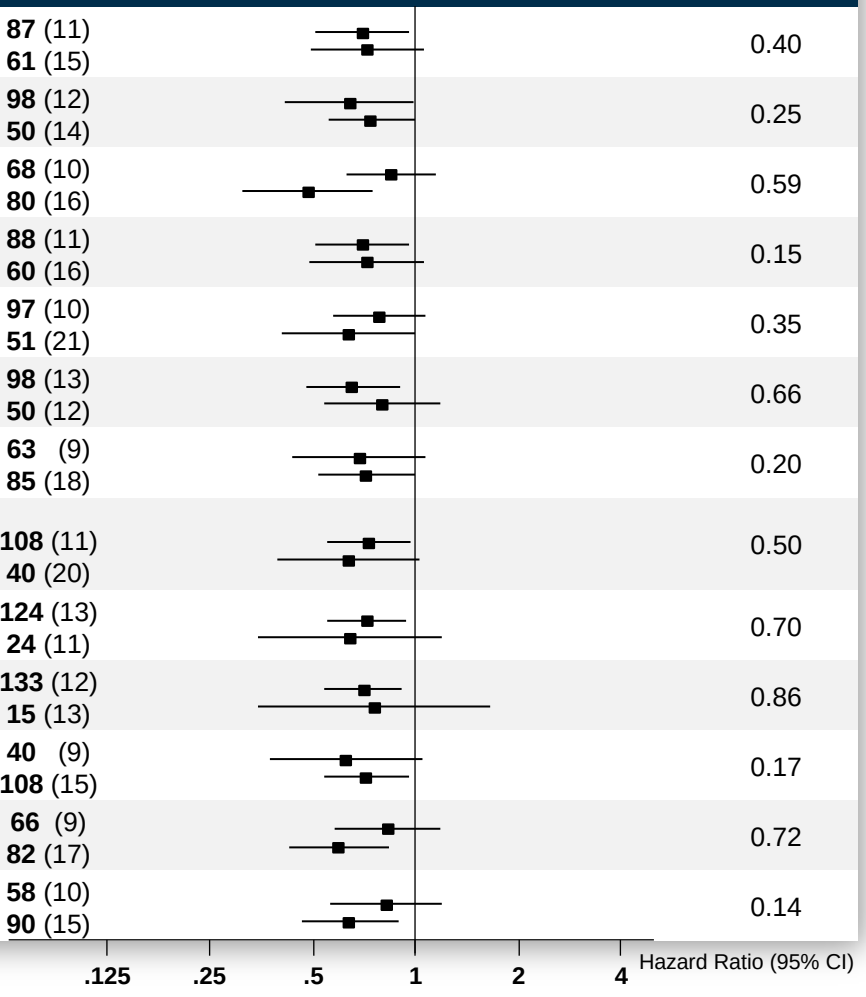


*ARC definite / probable.

Subgroups: Composite Safety Endpoint

(Cardiac Death, MI)

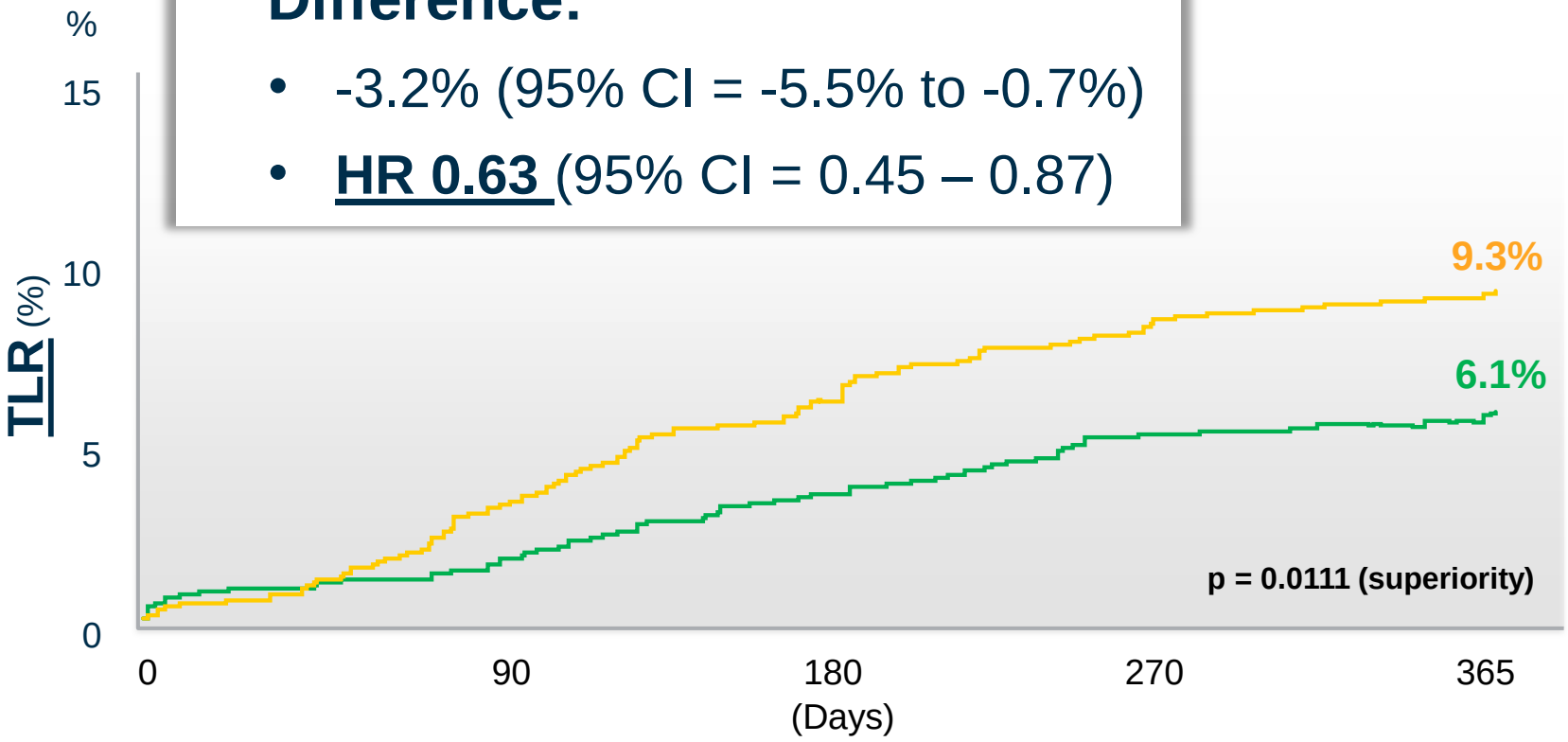
Category		N	DCS: Events (%)	BMS: Events (%)	P-value for Interaction
Age >80	No	1658	**69** (8)	**87** (11)	0.40
	Yes	756	**31** (10)	**61** (15)	
Female	No	1663	**72** (9)	**98** (12)	0.25
	Yes	751	**28** (8)	**50** (14)	
ACS at admission	No	1348	**47** (7)	**68** (10)	0.59
	yes	1066	**53** (10)	**80** (16)	
Diabetes	No	1609	**48** (6)	**88** (11)	0.15
	Yes	805	**52** (13)	**60** (16)	
Renal failure at admission	No	1992	**78** (8)	**97** (10)	0.35
	Yes	422	**22** (14)	**51** (21)	
Planed OAC at randomization	No	1573	**70** (9)	**98** (13)	0.66
	Yes	841	**30** (7)	**50** (12)	
Crusade score > median (35)	No	1396	**46** (7)	**63** (9)	0.20
	Yes	1018	**54** (11)	**85** (18)	
Anemia, transfusion / bleeding leading to hospitalization	No	1977	**74** (8)	**108** (11)	0.50
	Yes	437	**26** (12)	**40** (20)	
Planned major surgery in following year	No	2005	**87** (9)	**124** (13)	0.70
	yes	387	**12** (7)	**24** (11)	
Cancer in last 3 years	No	2181	**90** (9)	**133** (12)	0.86
	yes	231	**10** (9)	**15** (13)	
Multi-vessel disease at admission	No	770	**10** (3)	**40** (9)	0.17
	yes	1644	**90** (10)	**108** (15)	
Total stent length > 30 mm	No	1384	**42** (7)	**66** (9)	0.72
	Yes	1030	**58** (11)	**82** (17)	
Minimal stent diameter < 3 mm	No	1183	**47** (9)	**58** (10)	0.14
	Yes	1226	**53** (9)	**90** (15)	



Primary Efficacy Endpoint

Difference:

- -3.2% (95% CI = -5.5% to -0.7%)
- **HR 0.63** (95% CI = 0.45 – 0.87)

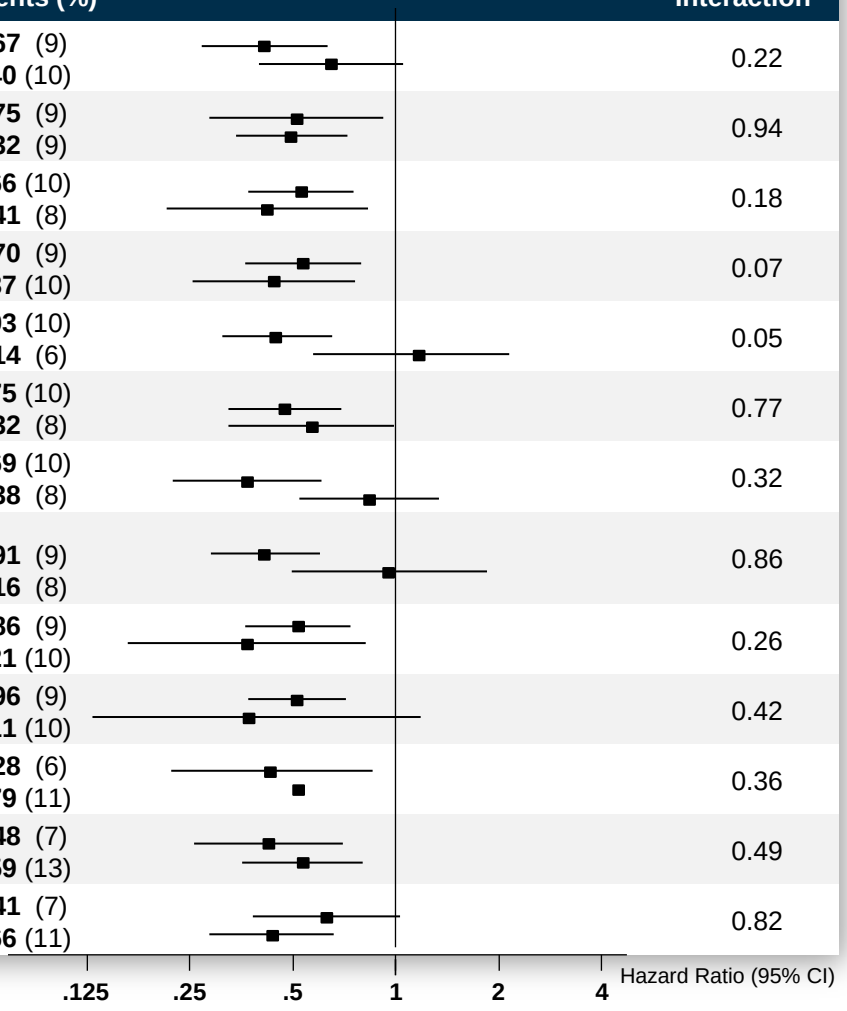


Number at Risk					
BMS	1,211	1,131	1,071	1,030	997
DCS	1,203	1,147	1,094	1,035	465

Subgroups Continued

Efficacy Endpoint (Clinically-driven TLR)

Category		N	DCS: Events (%)	BMS: Events (%)	P-value for Interaction
Age >80	No	1658	**51** (6)	**67** (9)	0.22
	Yes	756	**16** (5)	**40** (10)	
Female	No	1163	**46** (6)	**75** (9)	0.94
	Yes	751	**21** (7)	**32** (9)	
ACS at admission	No	1348	**33** (5)	**66** (10)	0.18
	yes	1066	**34** (7)	**41** (8)	
Diabetes	No	1609	**33** (5)	**70** (9)	0.07
	Yes	805	**34** (9)	**37** (10)	
Renal failure at admission	No	1992	**54** (6)	**93** (10)	0.05
	Yes	422	**13** (9)	**14** (6)	
Planed OAC at randomization	No	1573	**49** (7)	**75** (10)	0.77
	Yes	841	**18** (5)	**32** (8)	
Crusade score > median (35)	No	1396	**35** (5)	**69** (10)	0.32
	Yes	1018	**32** (7)	**38** (8)	
Anemia, transfusion / bleeding leading to hospitalization	No	1977	**55** (6)	**91** (9)	0.86
	Yes	437	**12** (6)	**16** (8)	
Planned major surgery in following year	No	2005	**59** (6)	**86** (9)	0.26
	yes	387	**7** (4)	**21** (10)	
Cancer in last 3 years	No	2181	**63** (6)	**96** (9)	0.42
	yes	231	**4** (4)	**11** (10)	
Multi-vessel disease at admission	No	770	**7** (2)	**28** (6)	0.36
	yes	1644	**60** (7)	**79** (11)	
Total stent length > 30 mm	No	1384	**23** (4)	**48** (7)	0.49
	Yes	1030	**44** (9)	**59** (13)	
Minimal stent diameter < 3 mm	No	1183	**23** (4)	**41** (7)	0.82
	Yes	1226	**44** (8)	**66** (11)	



Summary

- Dedicated design elements of the BioFreedom™ stent such as the absence of a polymer matrix together with a highly-lipophilic drug constitute a design rationale for shortening DAPT to 1M.
- By 1M, 98% of the drug content has been transferred leaving a BMS-like implant behind.
- The absence of a polymer leads to rapid healing and avoids detrimental effects such as hypersensitivity and local inflammation.
- Endothelialization is not delayed and similar to BMS in animal models
- Design elements of the BioFreedom™ stent lead to the safety of a BMS with the efficacy of a DES.

Conclusions

- ✓ At 2 years, the use of a BA9-DCS remained both significantly safer and more effective than a control BMS in HBR patients treated with one-month only DAPT
- ✓ No subgroup was identified for which use of a BMS was superior to a DCS
- ✓ From LEADERS FREE II trial,
  - Designed to support essential registration decision for polymer-free Biolimus A9™ coated stent in North America
  - Demonstrated reproducibility of Leaders Free findings of superior safety (1 year death, MI) and efficacy (1 year TLR) vs. BMS

Thank You !