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Análise Crítica do Estudo Leaders É o melhor stent que temos?

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Médico Setor de Hemodinâmica Hospital São Lucas





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CONFLITO DE INTERESSE

- **Não há conflito de interesse relacionado a esta apresentação**



Preditores de Sangramento Pós ICP

- Idade Superior a 75 anos
- Sexo Feminino *
- Anemia
- Doença Renal Crônica
- IMC baixo, HAS, DM e SCA.

REPLACE-2 (ICP Eletiva ou SCA)
Heparina + IIb/IIIa e Bivalirudina + IIb / IIIa

6.001 pacientes 3,2% HEMORRAGIA GRAVE

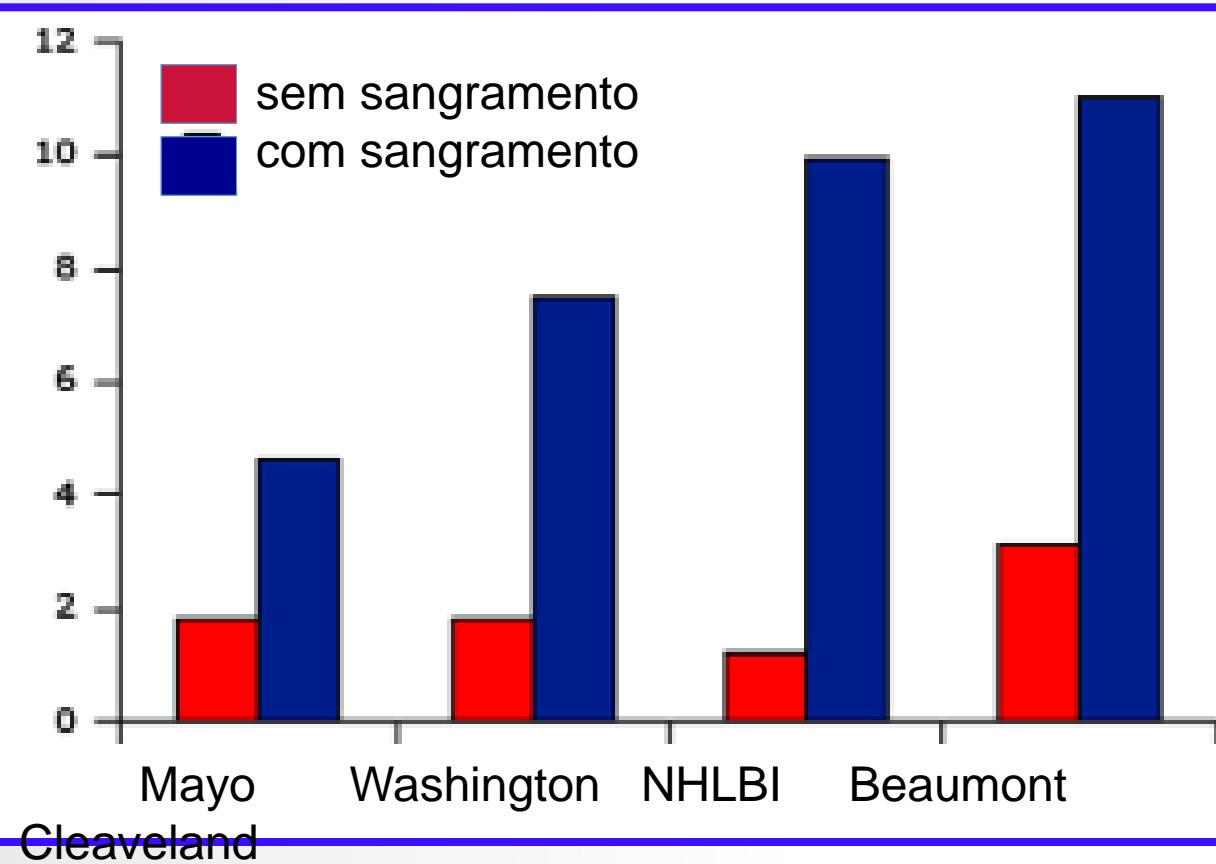
Voeltz F, J Cardiol. 2007; 100 (9): 1364.

Chacko M Am Heart J. 2006;151(5):1032.

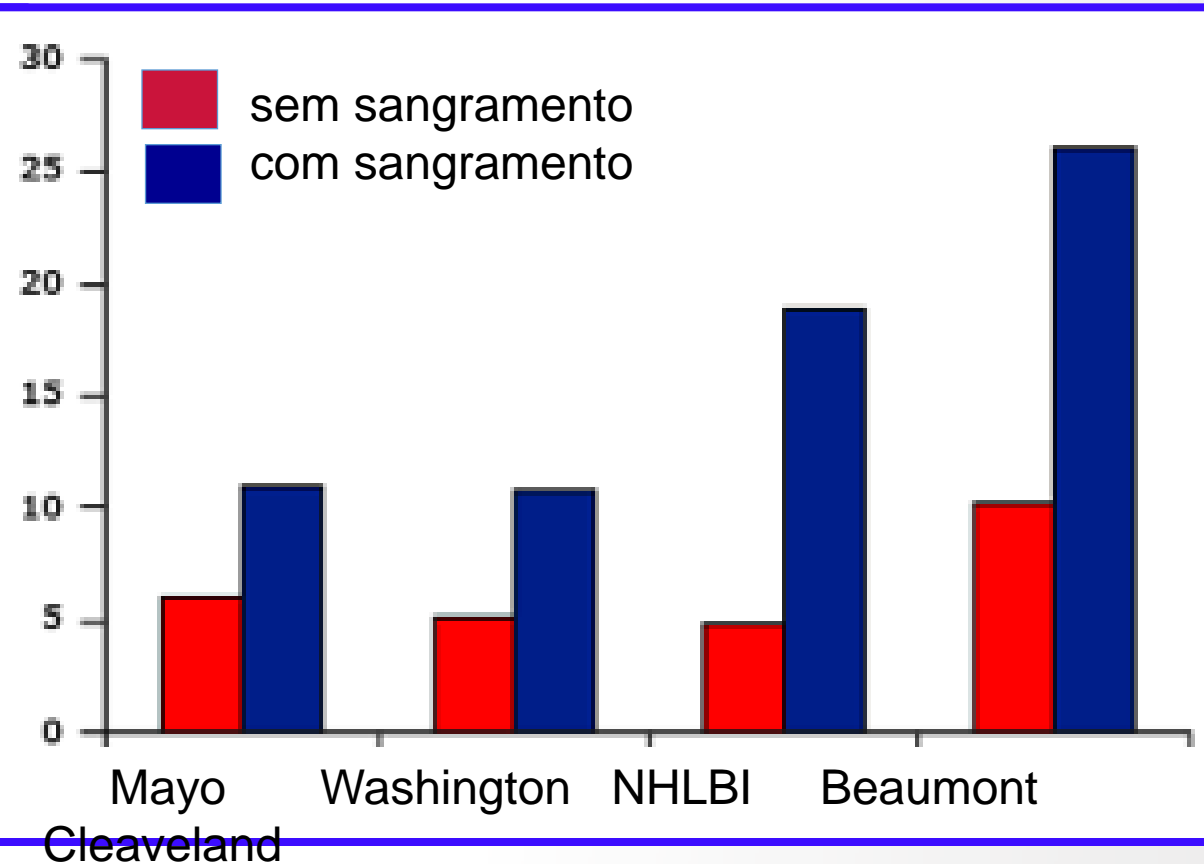
Fernandes LS. ESPRIT investigators JAm Coll Cardiol. 2002;40(6):1085.



Mortalidade Hospitalar e em 1 Ano



HOSPITALAR



TARDIA



Definição de Sangramento

BARC - Bleeding Academic Research Consortium

TIPO 0	Ausência de sangramento
TIPO 1	Sem atendimento ou suspensão de medicamentos
TIPO 2	Sangramento acionável e perceptível. Sem precisar de intervenção



Definição de Sangramento

BARC - Bleeding Academic Research Consortium

**TIPO 3A
SANGRAMENTO ATIVO**

Queda hemoglobina de 3 a <5 g / dL
Qualquer transfusão

**TIPO 3B
SANGRAMENTO ATIVO**

Queda hemoglobina \geq 5 g / dL
Tamponamento cardíaco
Necessidade cirurgia (exclui dental, nasal, pele, hemorróida)
Necessidade de agentes vasoativos

**TIPO 3C
SANGRAMENTO ATIVO**

Hemorragia intracraniana
Sangramento intra-ocular comprometendo a visão

Definição de Sangramento

BARC - Bleeding Academic Research Consortium

TIPO 4
SANGRAMENTO ATIVO
NA C.R.M.

Hemorragia intracraniana em 48 h
Reoperação para de controlar o sangramento
Transfusão de sangue ≥ 5 Unidades
Dreno de tórax ≥ 2 L dentro em 24 h

TIPO 5A
HEMORRAGIA FATAL PROVÁVEL

Provável; sem confirmação de autópsia ou imagem, Clinicamente suspeito

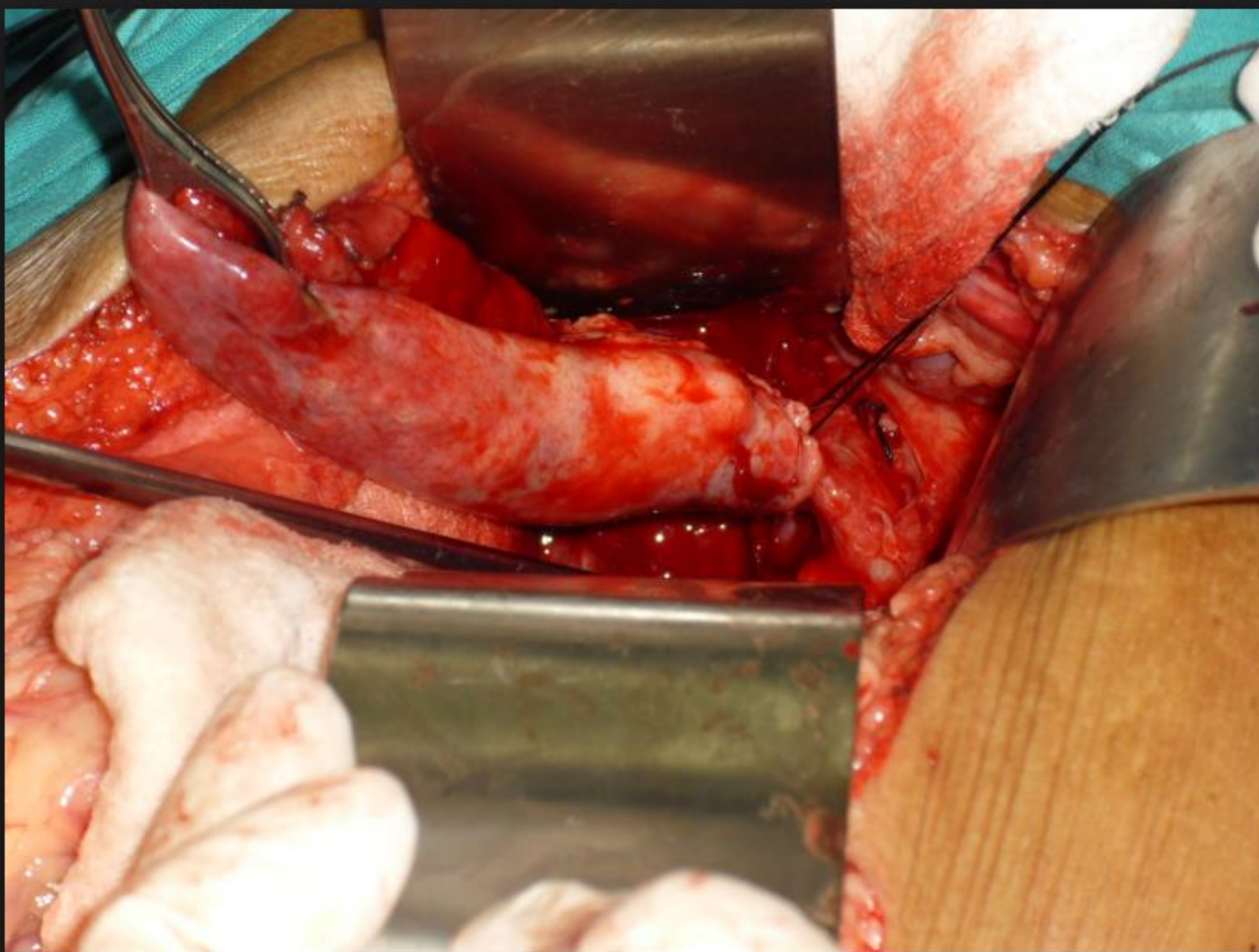
TIPO 5B
HEMORRAGIA FATAL
DEFINIDA

Sangramento ostensivo ou autópsia ou confirmação de imagem




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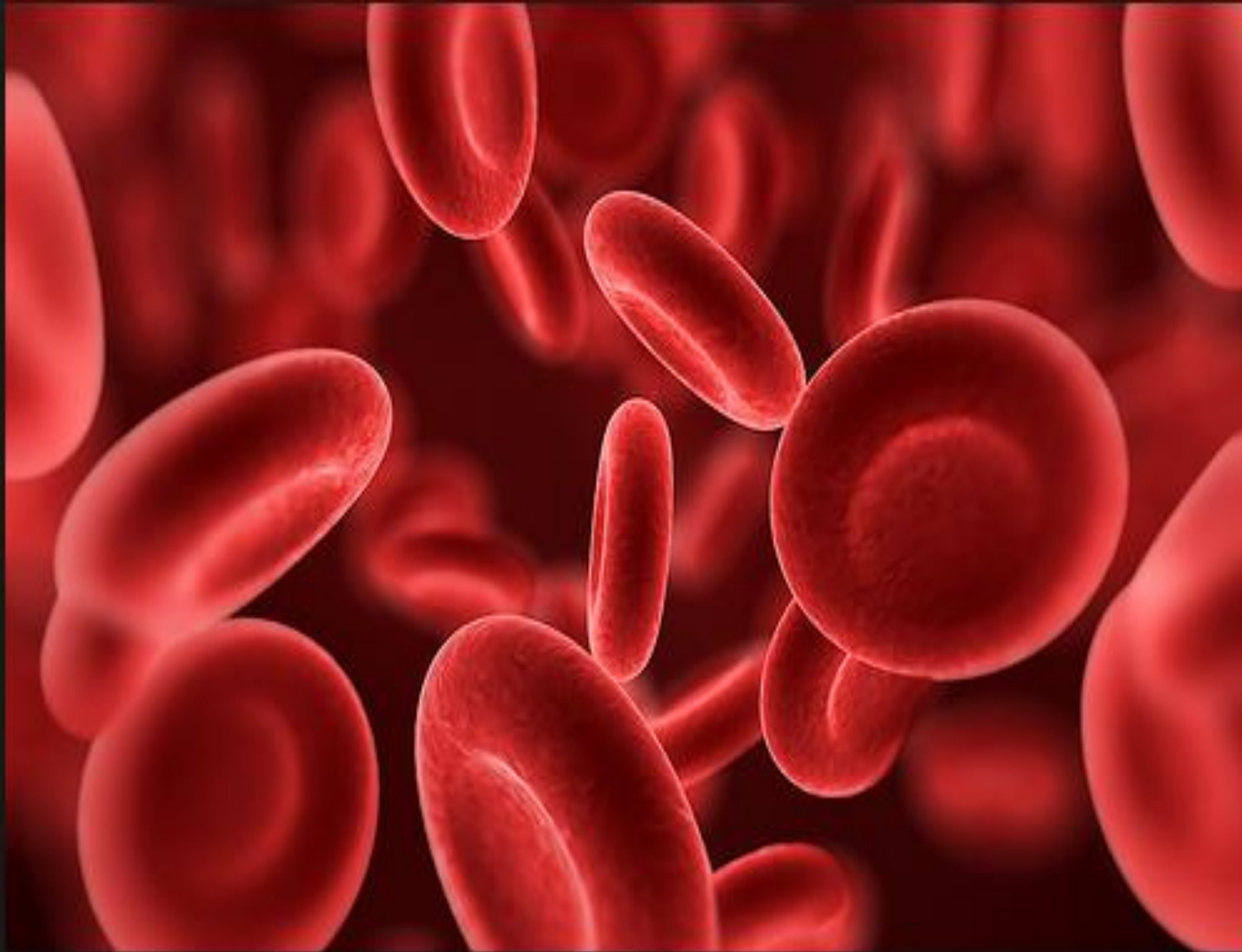
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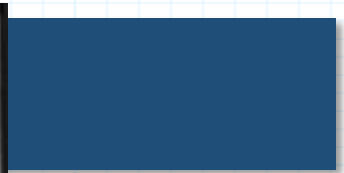
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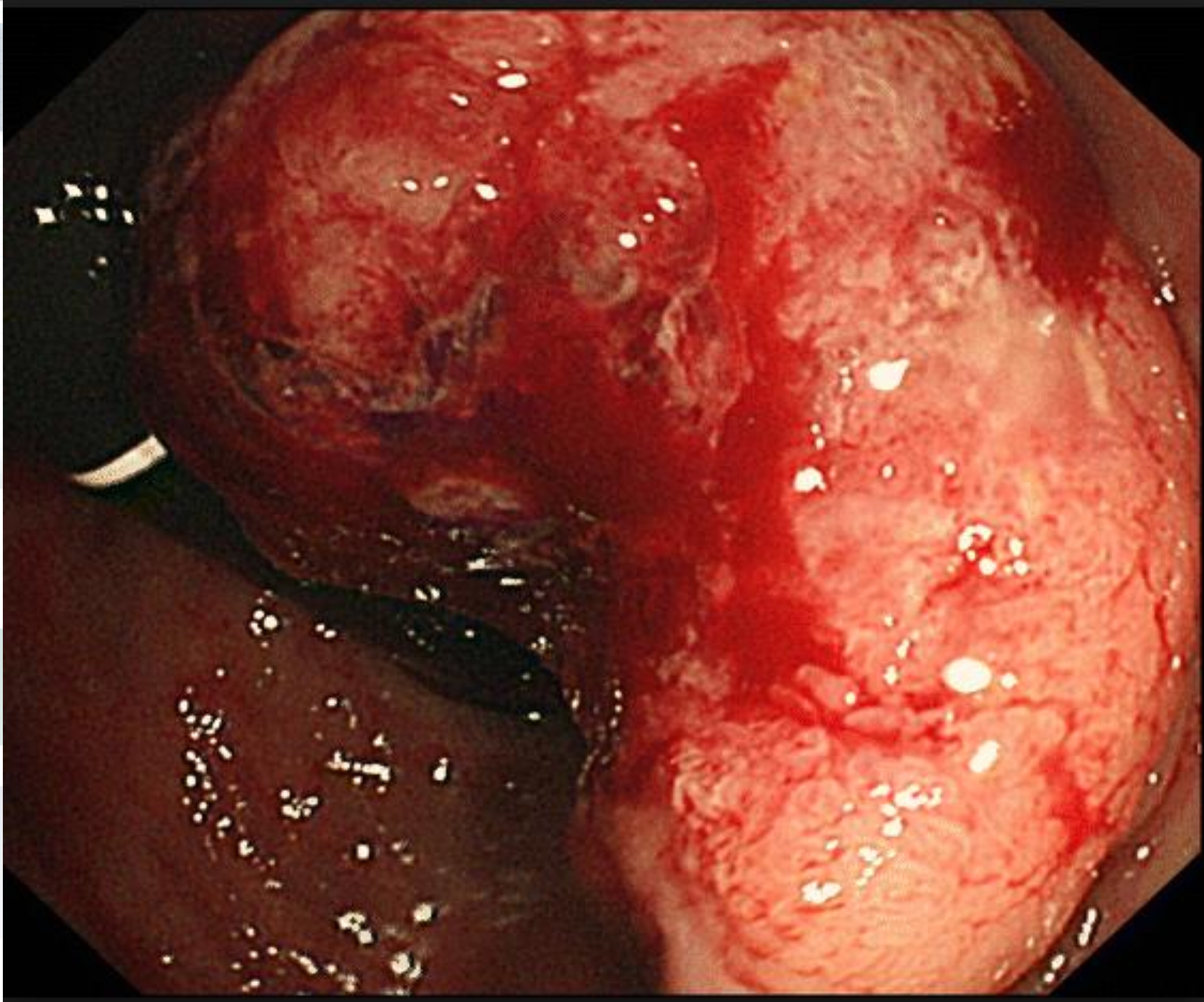
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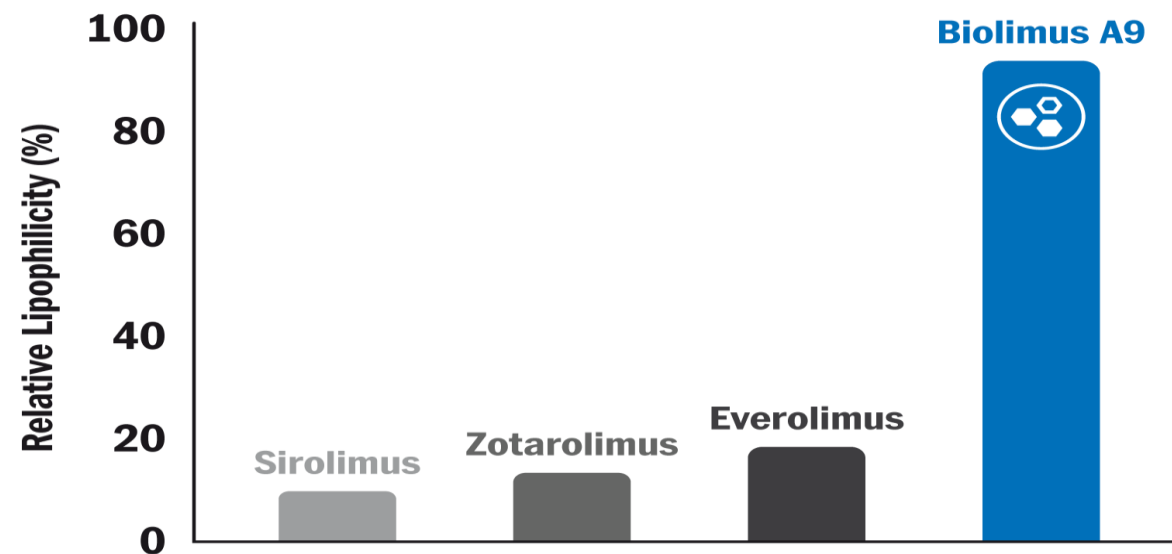
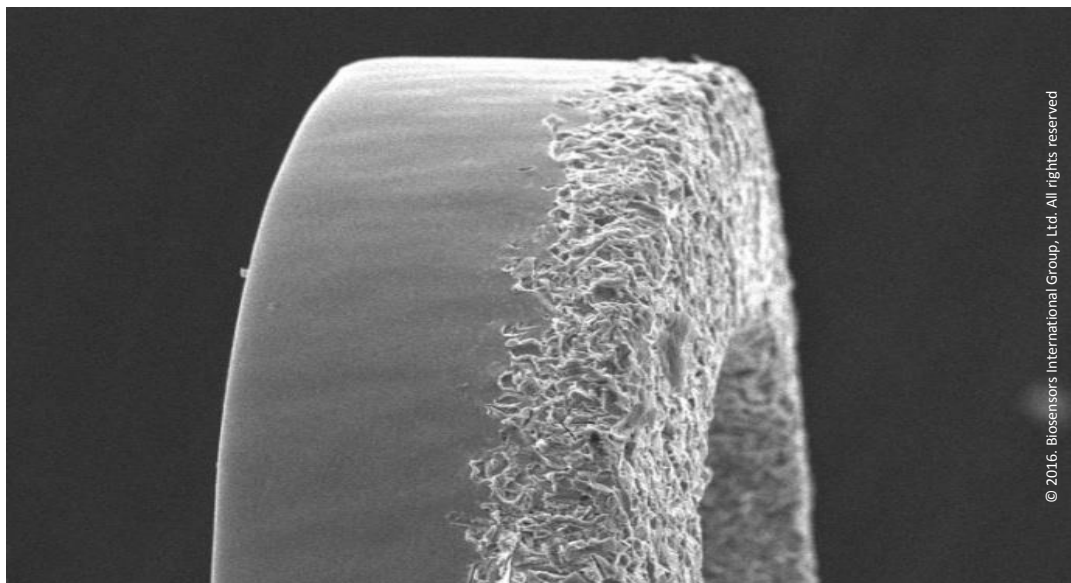
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BioFreedom™ Drug Coated Stent (DCS)

LEADERS FREE



+/- 2.8% (valid for all drugs tested). Data on file at Biosensors.¹

Vantagens potenciais

- Evitar quaisquer possíveis efeitos adversos relacionados com o polímero
- transferência de droga rápida à parede do vaso (98% dentro de um mês)
- DAPT pode ser reduzido para um mês em pacientes alto risco de sangramento

1. Tada et al., Circ Cardiovasc Interv 2010;3;174-183 2 Urban P et al. Am Heart J 2013; 165: 704-9

BioFreedom FIM

180 total patients

First Cohort

Second Cohort

**4 Months follow up
75 patients**

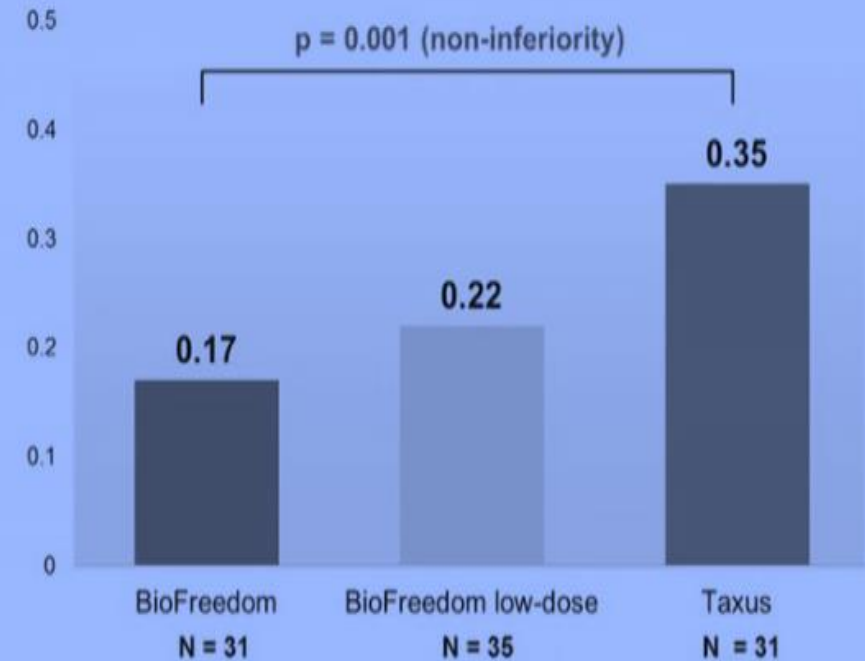
**12 Months follow up
105 patients**



**Enrollment Complete
Sept 2008 – Jan 2009**

**Enrollment Complete
Jan 2009 – Jun 2009**

Median In-Stent LLL at 12-month Follow-up 2nd Cohort – Primary Endpoint





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LEADERS *FREE*

Hypothesis

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

ORIGINAL ARTICLE

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



The NEW ENGLAND
JOURNAL of MEDICINE

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*

LEADERS FREE

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)

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

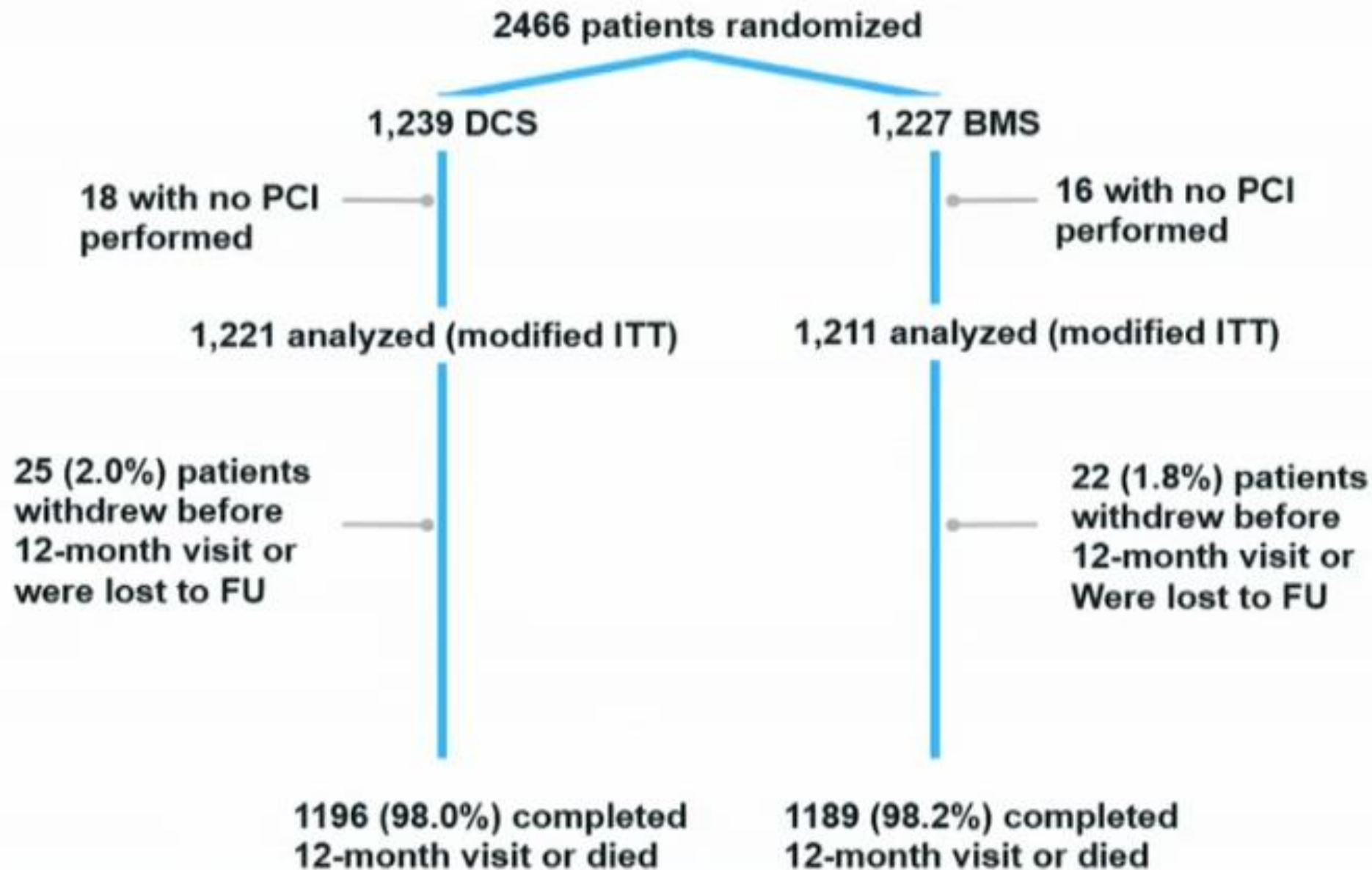
Both with one-sided alpha 0.025



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Enrollment and Follow-Up

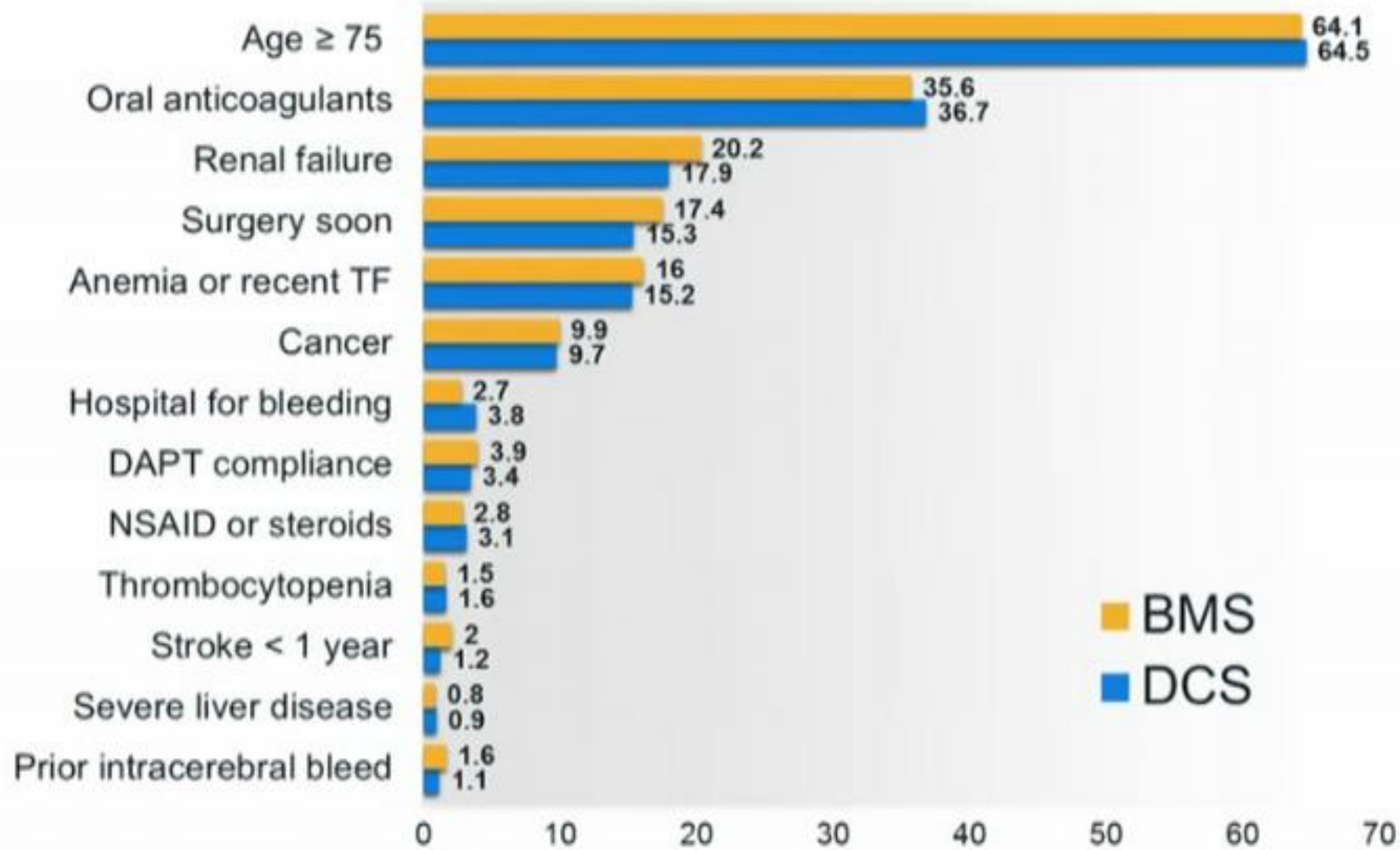




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Inclusion Criteria Applied (1.7 criteria / patient)





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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



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Index Procedure

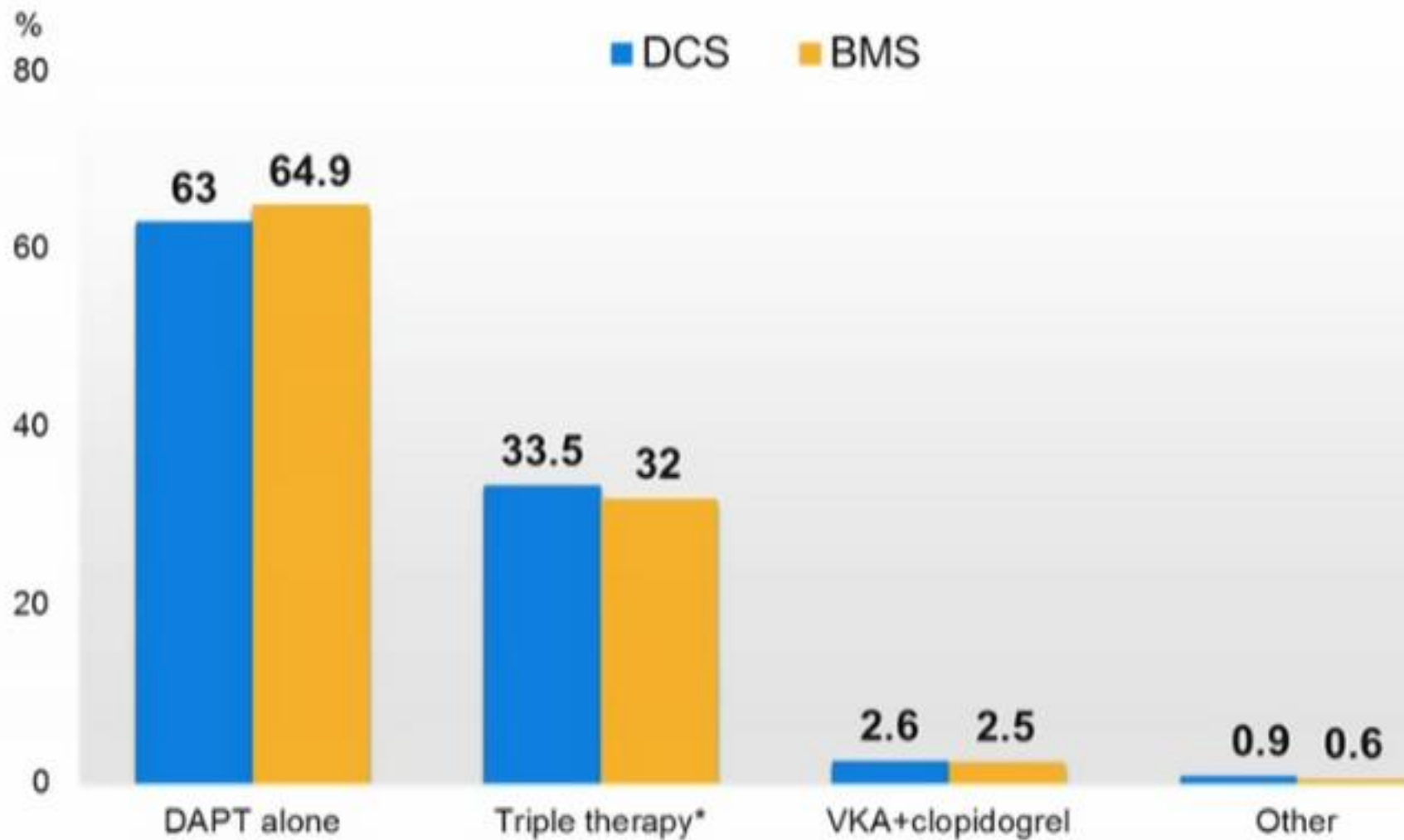
	DCS (%)	BMS (%)
Radial access	60.7	58.7
Staged procedure	4.5	5.9
Multi-lesion procedure	37.8	35.3
Multi-vessel procedure	21.8	21.4
Number of treated lesions / patient	1.6 ± 0.8	1.6 ± 0.9
LMS	3.0	3.9
SVG	1.4	1.8
Bifurcation	14.9	16.0
ISR	2.4	2.6
CTO	5.0	4.4



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Antithrombotic Medication at Discharge

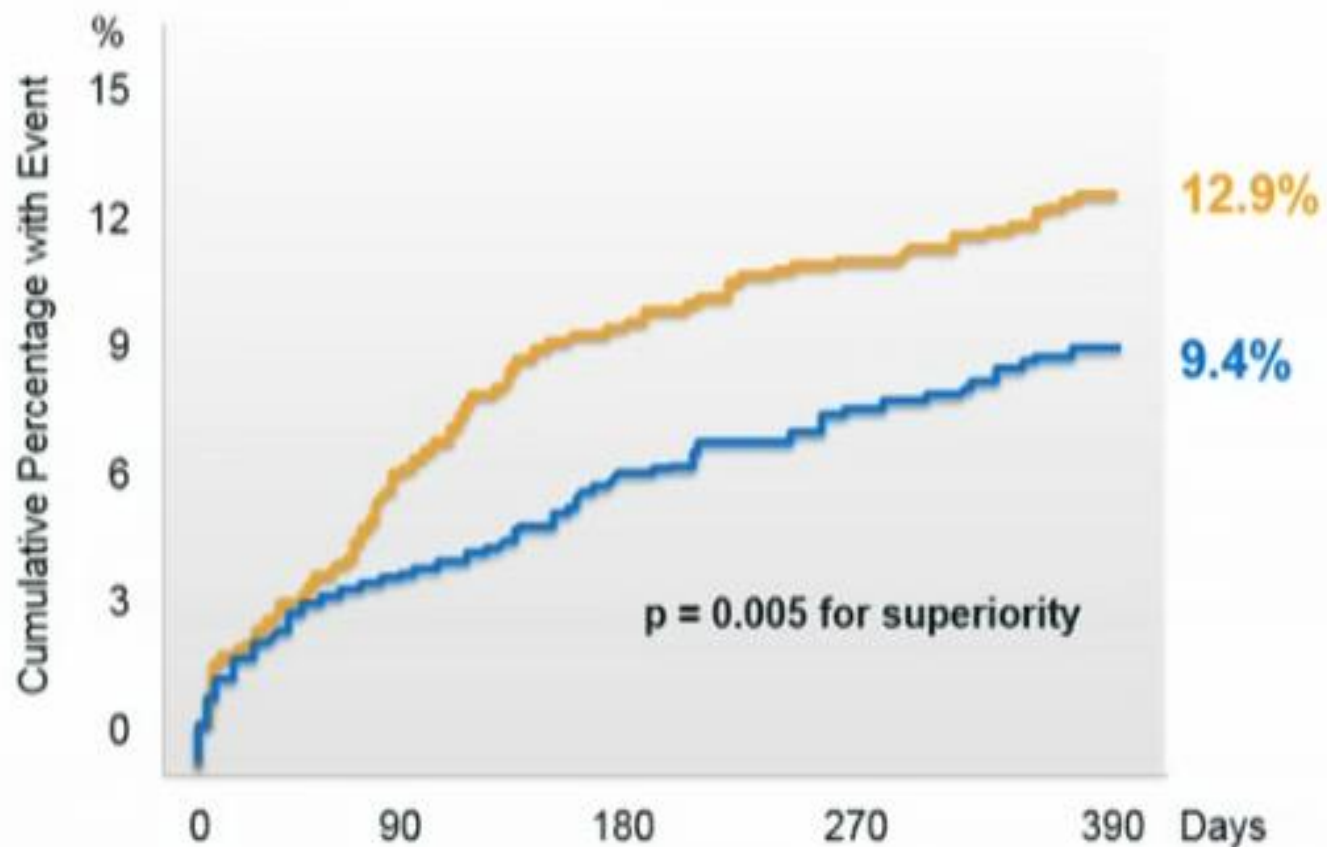




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Primary Safety Endpoint (Cardiac Death, MI, ST)



Number at Risk

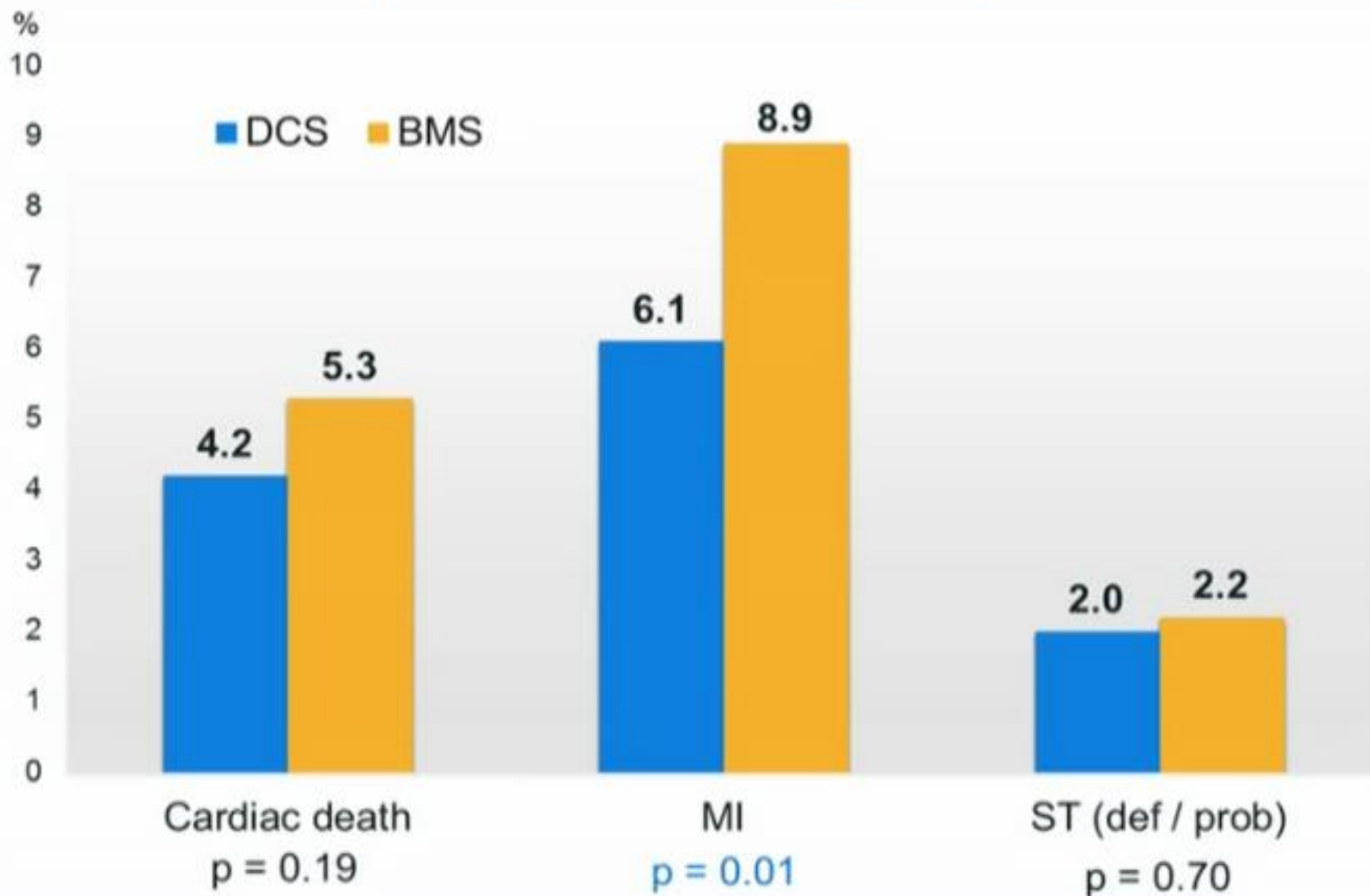
	0	90	180	270	390
DCS	1221	1146	1105	1081	1045
BMS	1211	1115	1066	1037	1000



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Components of Safety Endpoint

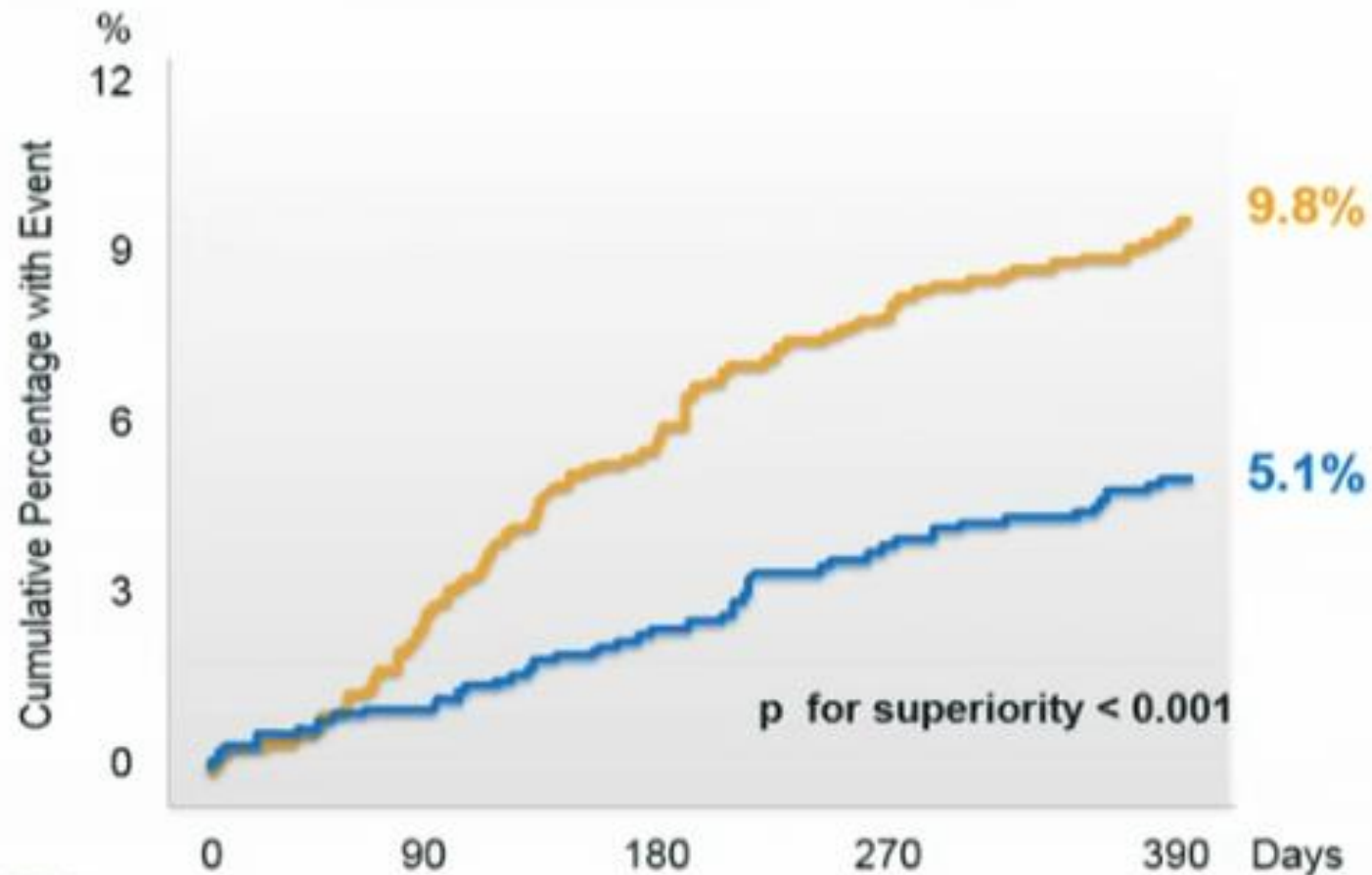




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Primary Efficacy Endpoint (Clinically-Driven TLR)



Number at Risk

	0	90	180	270	390
DCS	1221	1167	1130	1098	1053
BMS	1211	1131	1072	1034	984

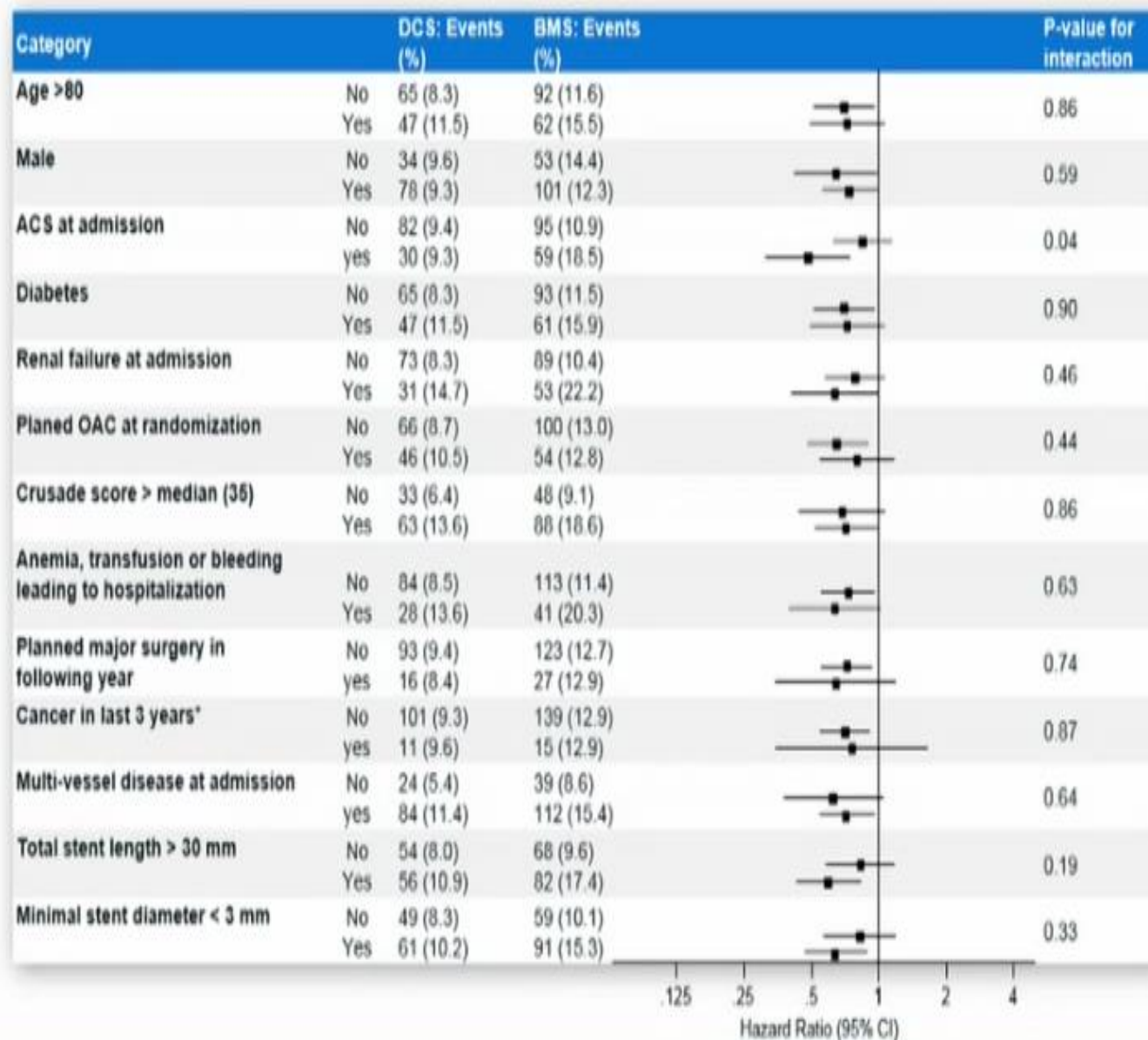


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Subgroups

Composite safety endpoint (cardiac death, MI, ST)



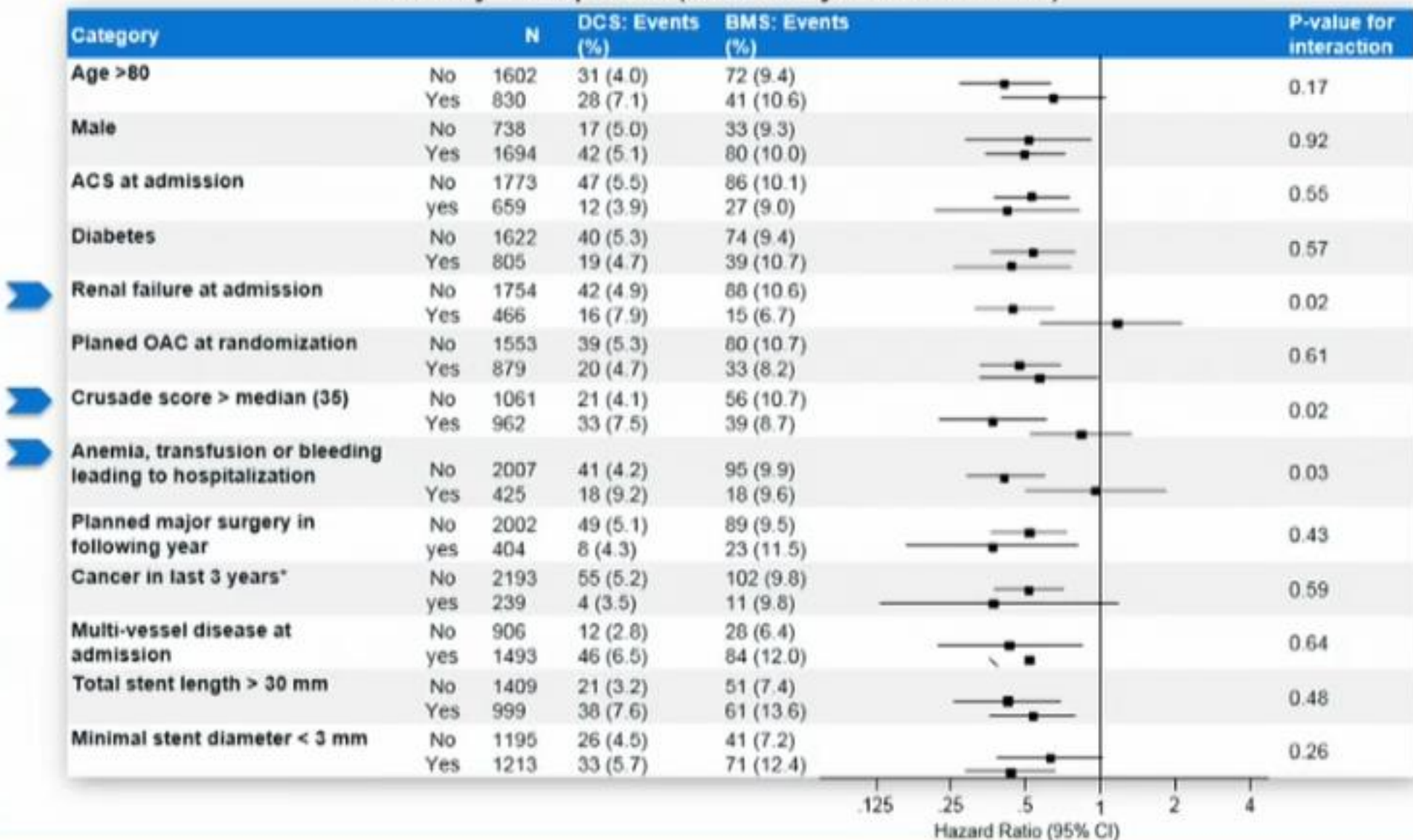


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Subgroups (continued)

Efficacy endpoint (clinically driven TLR)

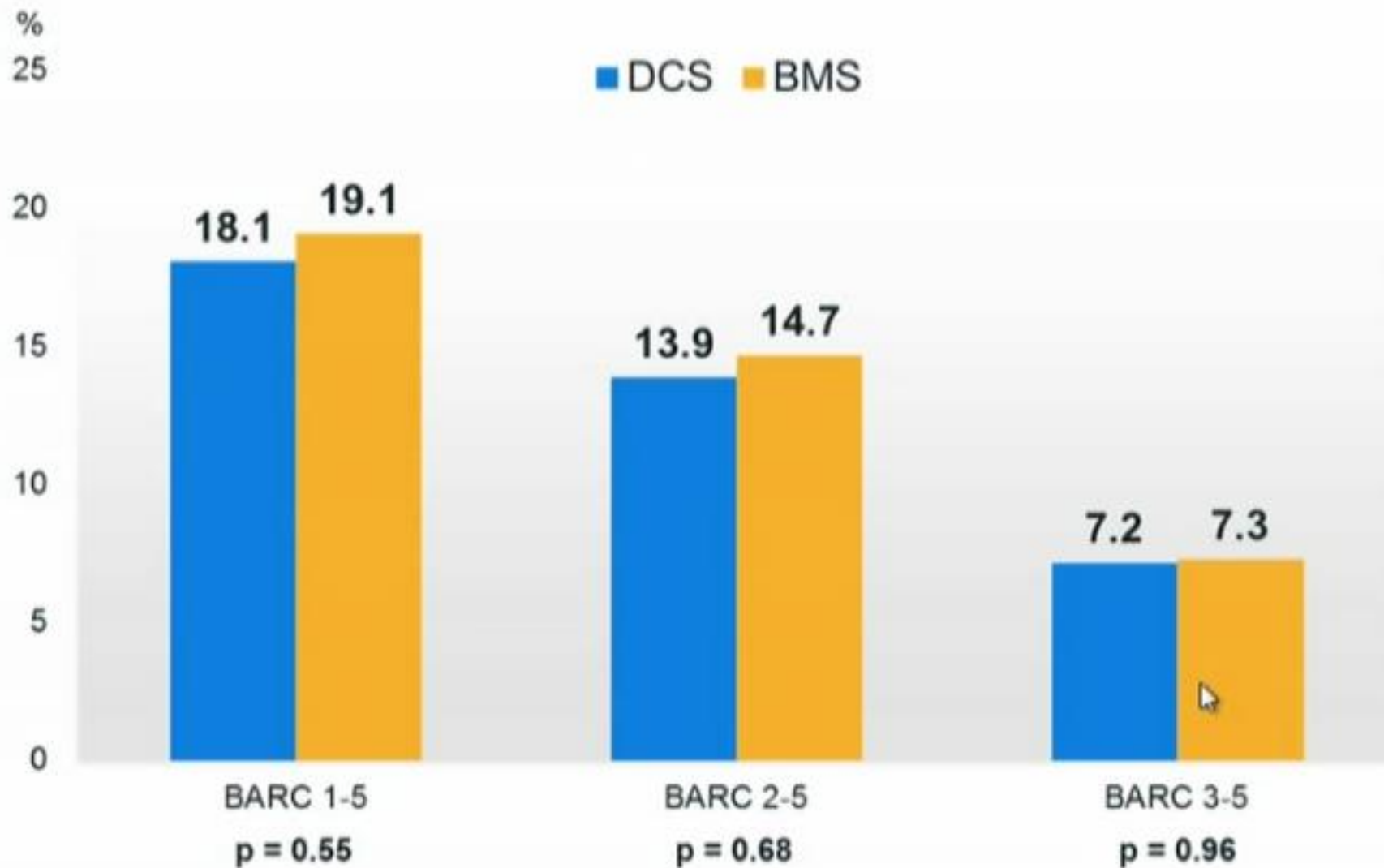




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Bleeding During 12 Months Follow-Up

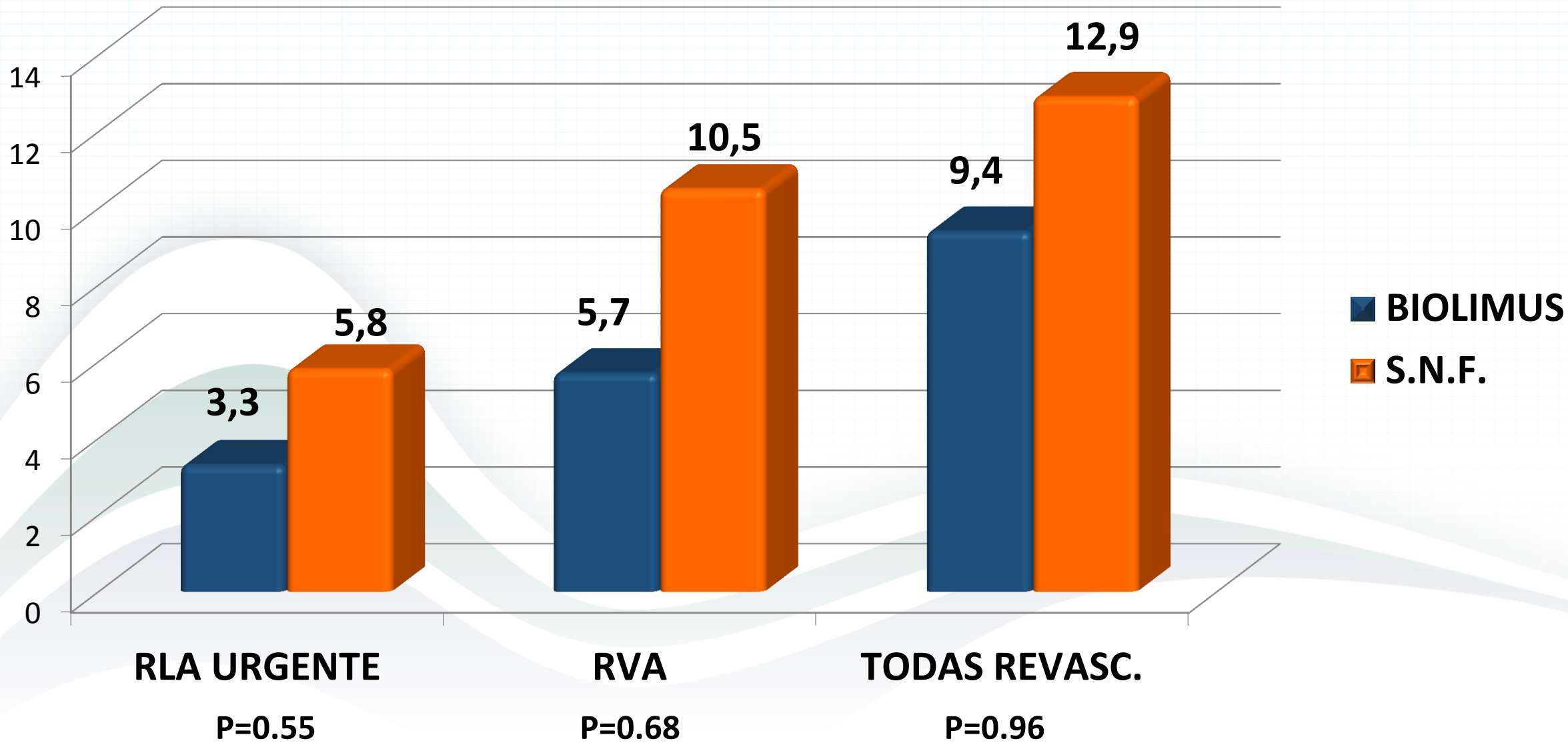




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DESFECHOS SECUNDÁRIOS DE EFICÁCIA

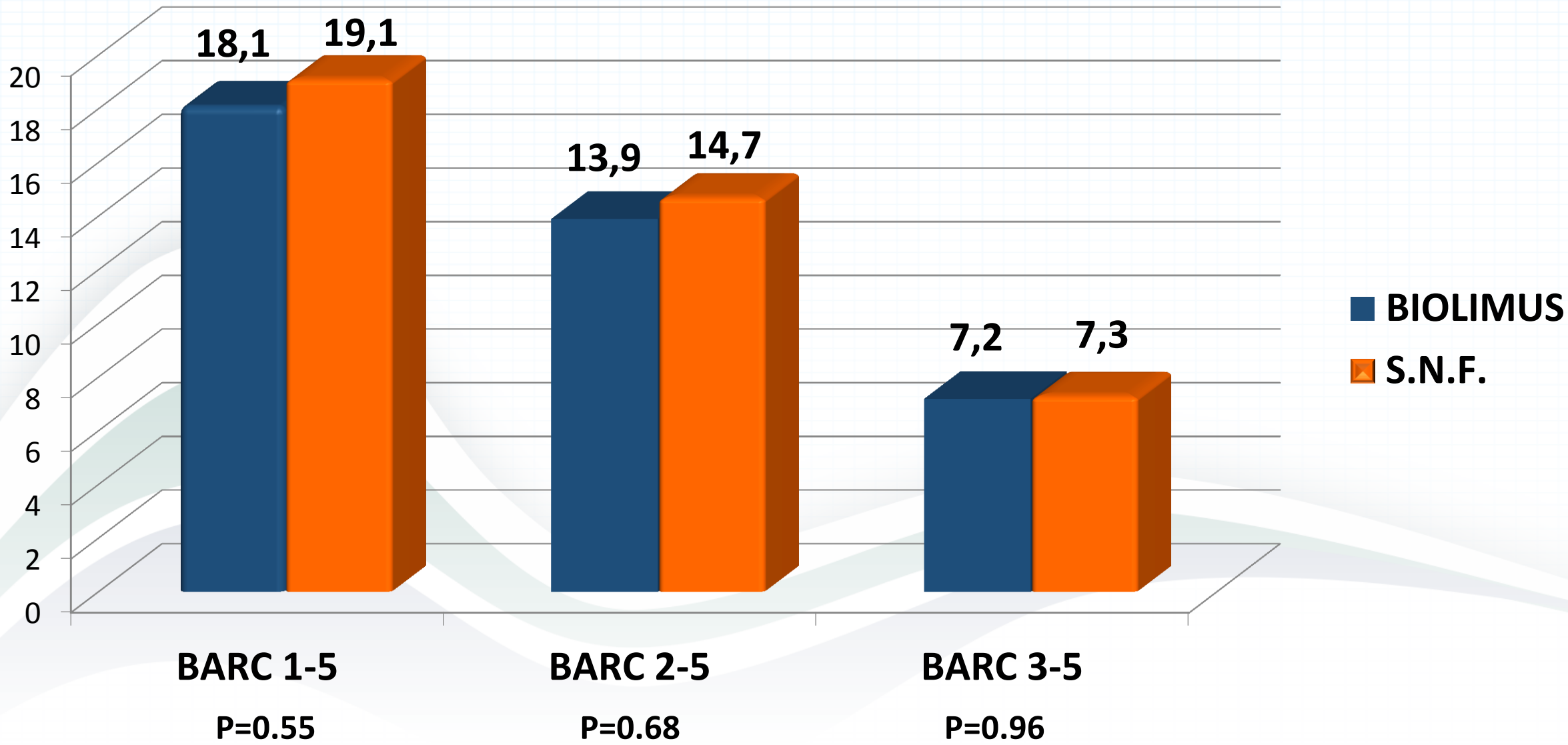




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SANGRAMENTO DURANTE O ACOMPANHAMENTO DE 12 MESES



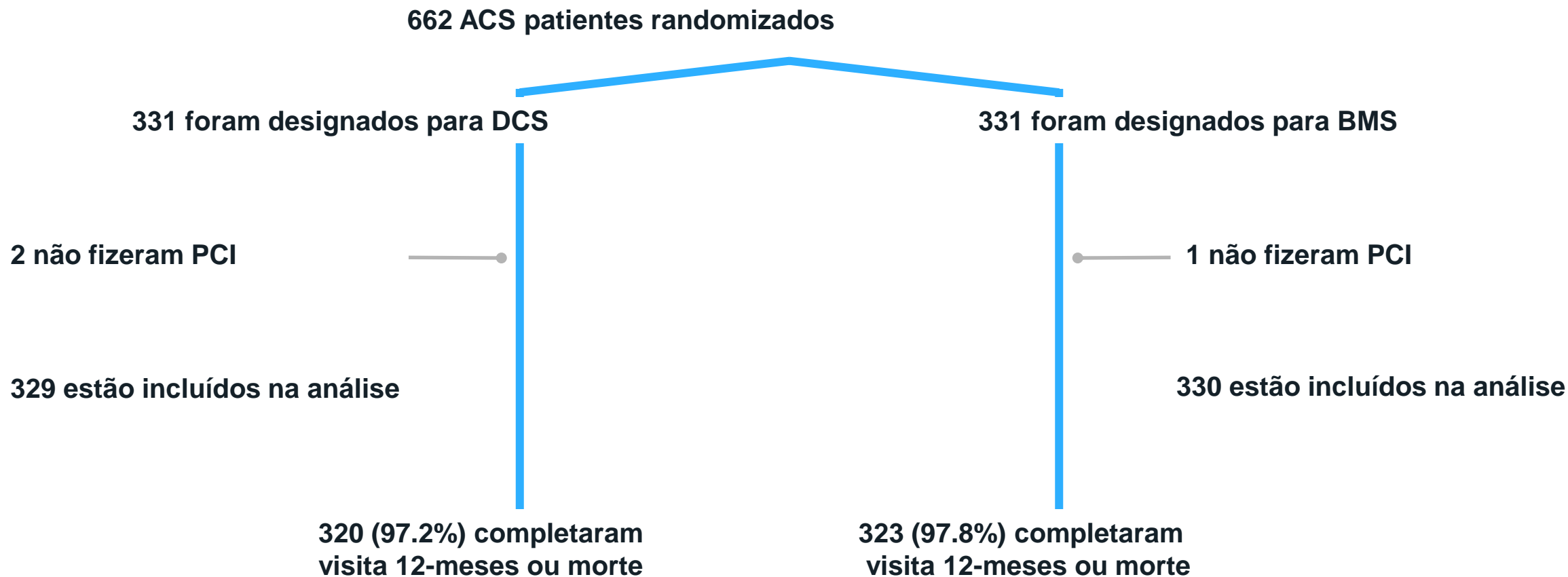


BIOSENSORS
INTERNATIONAL™

LEADERS FREE ACS

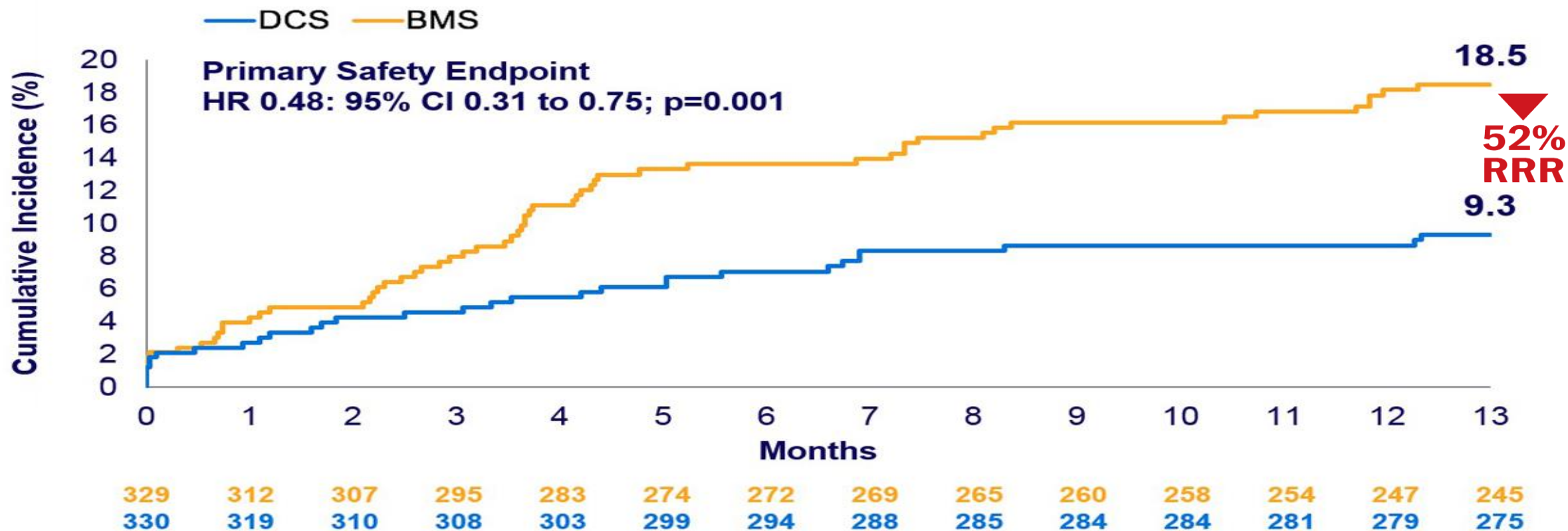
C.K. Naber, P. Urban, P.J. Ong, M. Valdes-Chavarri, A. Abizaid, S.J. Pocock,
F. Fabbocchi, C. Dubois, S. Copt, S. Greene
and M.C. Morice for the LEADERS FREE Investigators

Presented by CK Naber EuroPCR 17th May 2016



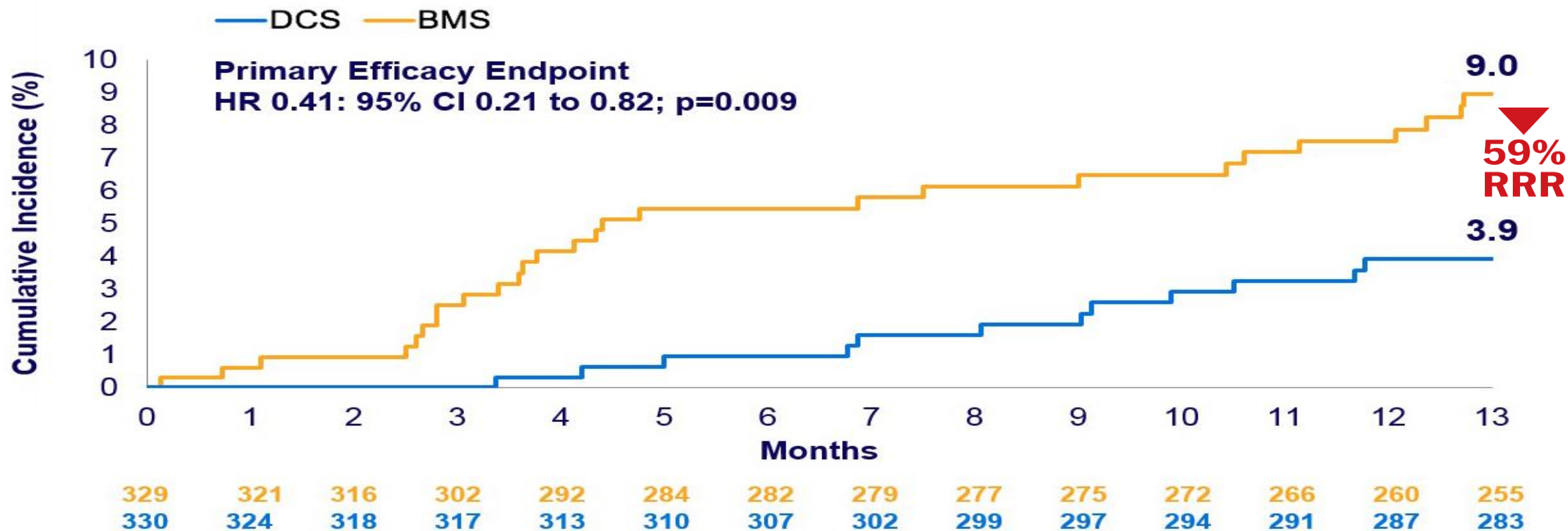
LEADERS FREE ACS

Morte cardíaca MI, or Def / Prob ST- 12 Meses FU



LEADERS FREE ACS

Revascularização da lesão alvo clinicamente indicada - 12 Meses FU





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

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

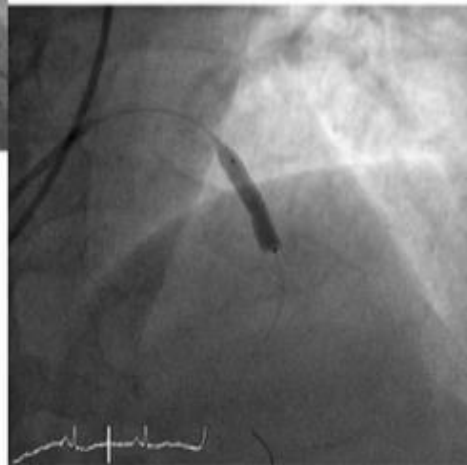


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1-VD disease
mid-LAD stenosis 80%
EF 65%



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





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Hereditary hemorrhagic telangiectasia

- Autosomal dominant fashion
- Abnormal blood vessel formation in the skin, mucous membranes and organs such as lungs, liver and brain
- Telangiectasias small vascular malformation - - -> Nosebleed (epistaxis) 90-95% of people
- Arteriovenous malformation (acute and chronic bleeding) in the lungs (50%), liver (30-70%) , brain (10%) and spinal cord (<1%)
- Association with other hemorrhagic disease (Willebrandt disease)



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Clinical Follow-Up at 1 year

- Epistaxis +++ ongoing (3X Blood transfusion)
- One hospitalization in Emergency department
- Hb level: 12g/dl
- No angina
- Stop Clopidogrel at day 30, on aspirin 80mg/d



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- **Primeiro ER dedicado a paciente com Alto Risco de Sangramento (A.R.S.)**
- **Envolveu os excluídos dos ER de ICP e Antiagregantes pela alta comorbidade relacionada ao ARS**
- **Pacientes com A.R.S. com DAP por apenas um mês o BioFreedom foi mais seguro e eficaz do que SNF, inclusive na SCA**



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- LEADERS FREE – CONCLUSÕES:

- **Primeiro ER dedicado a paciente com Alto Risco de Sangramento (A.R.S.)**
- **Maioria idosa com mais de uma comorbidade**
- **Envolveu os excluídos dos ER de ICP e Antiagregantes**
- **Pacientes com A.R.S. com DAP por apenas um mês o BioFreedom foi mais seguro e eficaz do que SNF.(excelente nas SCA)**

**ESTA É UMA RESPOSTA REAL, ATÉ AGORA
INEXISTENTE, SOBRE UMA NECESSIDADE CLÍNICA EM
PACIENTES COM ALTO RISCO DE SANGRAMENTO E A
POSSIBILIDADE DE SUBSTITUIÇÃO DEFINITIVA DOS SNF**



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É o melhor stent que temos?

- **Não podemos afirmar ser “O MELHOR STENT” por não ser testado com outros stents de nova geração.**

Mundo
faz nestes
orna INCOMPARA

É o melhor stent que temos?

ação.

- **Mas, ter sido o único comprovadamente seguro e eficaz nestes pt ARS, finalizando a era dos SNF o torna INCOMPARÁVEL!**



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MUITO OBRIGADO!



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- LEADERS FREE – CONCLUSÕES:

Conclusão I

Em pt ARS seguidos por 390 dias após ICP tratados com 1 Mês de DAP:

Sangramento maior foi frequente (7.2%)

Preditores trombóticos (IAM e TS): foi menos no SF (5,6% vs 8,6 %)

Mortalidade após sangramento maior e evento trombótico foi alta e comparável

Paciente com alto risco de sangramento foram em geral os de maior risco de trombose



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- LEADERS FREE – CONCLUSÕES:

Conclusão II

Nove preditores de trombose e/ou sangramento foram identificados para pt ARS

Preditores sangramento: baixa Hb. Uso de ACO na alta a acesso femoral

Preditores de trombose: I Renal, Multiarterial, Bifurcação e uso de SNF.

Preditores de ambos: idosos e uso de múltiplos stents

O Modelo é bom para sangramento mas limitado para discriminar trombose.



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- LEADERS FREE – CONCLUSÕES:

Mensagem final I

Leaders Free é importante ER de pt ARS que são dilemas clínicos excluídos de outros estudos

Introduziu uma verdadeira alternativa ao SNF

Superioridade em Segurança e Eficácia do SF sobre o SNF.

Na SCA (662pt) houve grande Superioridade em Segurança e Eficácia com do SF como tto de escolha



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- LEADERS FREE – CONCLUSÕES:

Mensagem final II

Leaders Free é importante ER de pt ARS que são dilemas clínicos excluídos de outros estudos

Sangramento alto ($\cong 7\%$) em ambos grupos, mas com mais trombozes e, SNF

Mortalidade alta após trombose ou sangramento.

Trombose e sangramento frequentemente ocorreu no mesmo paciente.

Qualificações: ampla definição de ARS, elevada TS em 1 ano (2.2%), elevado desfecho de segurança do tipo IAM 2^{ário} a RIS nos SNF



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LEADERS FREE – Impact on Clinical Practice *Take Away and Close*

DO I NEED TO CHANGE MY PRACTICE?

Yes!!!

1. increased attention to the category of HBR patients
2. NO MORE BMS! For the time being, Biofreedom is the best alternative for short-term DAPT (although would encourage further studies with “best” current DES platforms)