

# LEADERS FREE



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## **Gender-based outcomes in patients at high bleeding risk: Results from the LEADERS FREE randomized controlled trial**

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Presented by R. Mehran EuroPCR 2018

## Why this sub-study?

- Women undergoing percutaneous coronary intervention (PCI) are traditionally at high bleeding risk (HBR), and consequently may be undertreated with PCI and with drug eluting stents (DES).
- We sought to assess the patient characteristics and 2-year clinical outcomes in a pre-specified analysis by sex from the LEADERS FREE randomized controlled trial of HBR patients and examined for treatment interaction by stent type.

# LEADERS FREE Trial Design

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

BioFreedom™  
DCS

VS.

Gazelle™  
BMS

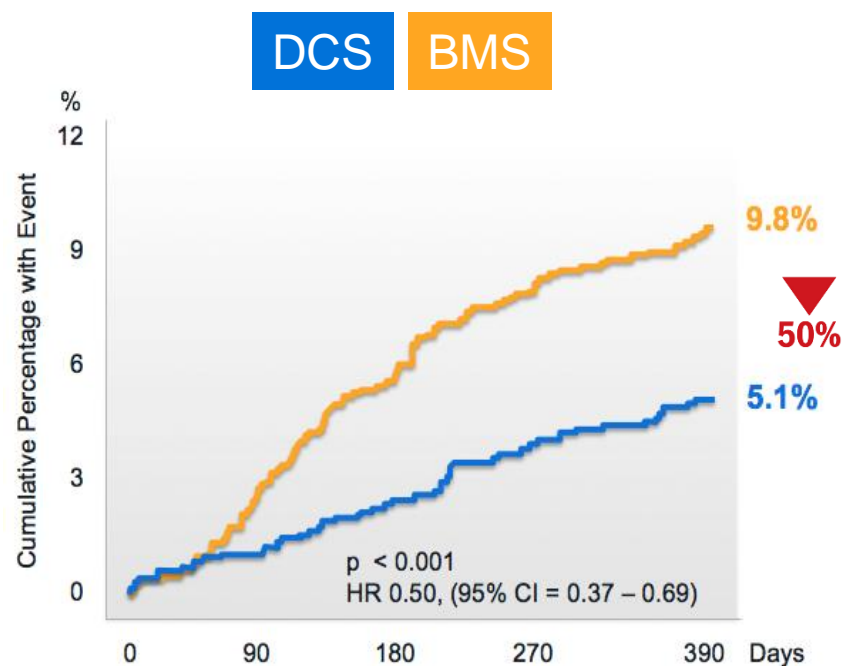
**DAPT mandated for 1 month only, followed by long-term SAPT**

- **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)

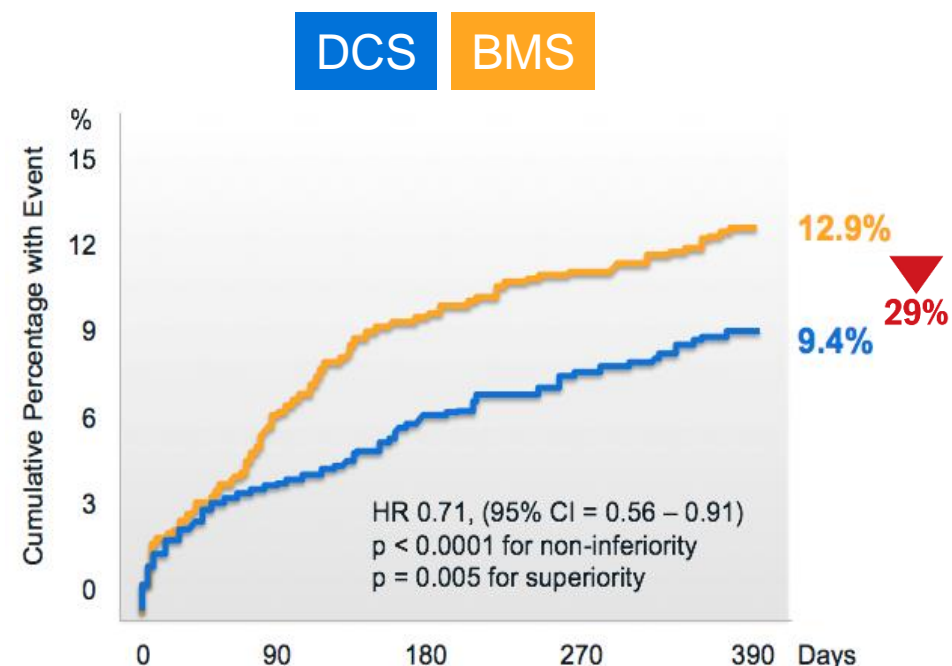
SAPT=Single antiplatelet therapy

# LEADERS FREE co-primary outcomes

## Efficacy (clinically driven TLR)



## Safety (cardiac death, MI, ST)



# Inclusion criteria by gender

Eligibility criteria	Male (N=1694)	Female (N=738)	P-value
Age ≥75 Years Old	998 (58.9%)	566 (76.7%)	<0.001
Oral anticoagulation planned to continue after PCI	640 (37.8%)	239 (32.4%)	0.0109
Hemoglobin <11 g/liter or transfusion within 4 wk before randomization	248 (14.6%)	131 (17.8%)	0.0518
Platelet count <100,000/mm <sup>3</sup>	31 (1.8%)	7 (0.9%)	0.1071
Hospital admission for bleeding in previous 12 mo	63 (3.7%)	16 (2.2%)	0.0473
Stroke in the last 12 Months	32 (1.9%)	7 (0.9%)	0.0896
Prior Intracerebral Bleed	27 (1.6%)	6 (0.8%)	0.1260
Severe chronic liver disease	17 (1%)	4 (0.5%)	0.2581
Creatinine clearance <40 ml/min	286 (16.9%)	178 (24.1%)	<0.001
Non-Skin Cancer in the previous 3 Years	187 (11%)	52 (7%)	0.0024
Planned major surgery in next 12 mo	301 (17.8%)	97 (13.1%)	0.0046
Glucocorticoids or NSAID planned for >30 days after PCI	44 (2.6%)	28 (3.8%)	0.1094
Expected nonadherence to >30 days of dual antiplatelet therapy	70 (4.1%)	18 (2.4%)	0.0398

Superiority p=<0.05

# Baseline characteristics by gender

Patient level characteristics	Male (N=1694)	Female (N=738)	P-value
Age (years)	74.51 ± 9.49	78.31 ± 8.37	<0.001
Heart rate (bpm)	70.09 ± 14.38	72.20 ± 13.62	<0.001
Systolic blood pressure (mmHg)	136.13 ± 22.56	138.12 ± 24.35	0.0794
Diastolic blood pressure (mmHg)	73.66 ± 12.82	70.63 ± 13.47	<0.001
Diabetes mellitus	559 (33.1%)	246 (33.4%)	0.8601
• Insulin treatment	169 (30.2%)	93 (37.8%)	0.0422
Current smoker	221 (13.1%)	50 (6.8%)	<0.001
Renal insufficiency	350 (20.7%)	174 (23.8%)	0.0841
Dyslipidemia	1027 (61.7%)	461 (63.9%)	0.2960
Hypertension	1293 (76.5%)	620 (84.2%)	<0.001
Previous stroke	164 (9.7%)	78 (10.6%)	0.5073
CHF	226 (13.4%)	99 (13.5%)	0.9572
Prior MI	372 (22.1%)	123 (16.8%)	0.0030
Prior PCI	404 (23.9%)	131 (17.8%)	0.0009
Prior CABG	193 (11.4%)	44 (6%)	<0.001
PAD	280 (16.7%)	100 (13.7%)	0.0653
Malignancy	186 (11%)	53 (7.2%)	0.0038
Atrial fibrillation	596 (35.3%)	246 (33.4%)	0.3703
COPD	208 (12.4%)	64 (8.8%)	0.0107
Multivessel disease	1082 (64.8%)	411 (56.5%)	0.0001

CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive lung disease; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction

Superiority p=<0.05

# PCI indication and by gender

PCI indication	Male (N=1694)	Female (N=738)	P-value
Stable angina	663 (39.1%)	273 (37%)	p=0.3397
Silent ischemia	355 (21%)	112 (15.2%)	p=0.0010
Unstable angina	249 (14.7%)	121 (16.4%)	p=0.3126
Acute coronary syndrome	427 (25.2%)	232 (31.4%)	p=0.0017
• STEMI	69 (16.2%)	36 (15.5%)	p=0.429
• NSTEMI	358 (83.8%)	196 (84.5%)	p=0.0039

NSTEMI, non-ST segment elevation myocardial infarction;  
STEMI, ST-segment elevation myocardial infarction;

# Lesion level characteristics by gender

Lesion level characteristics	Male (N=2714)	Female (N=1123)	p-value
Lesion length	17.68 ± 9.8	16.48 ± 8.4	0.0012
Reference vessel diameter	3.01 ± 0.5	2.95 ± 0.5	0.0003
Pre-procedure stenosis	82.02 ± 12.3	80.79 ± 12.1	0.0344
Small vessel disease	791 (29.2%)	374 (33.3%)	0.0167
Long lesion (> 30mm)	175 (6.5%)	57 (5.1%)	0.0989
Pre-procedure TIMI flow			0.1755
0	121 (4.5%)	34 (3%)	
1	95 (3.5%)	52 (4.6%)	
2	182 (6.7%)	55 (4.9%)	
3	2314 (85.3%)	981 (87.4%)	
Lesion class (ACC/AHA class)			0.0022
A	364 (13.9%)	191 (17.7%)	
B1	967 (37%)	418 (38.6%)	
B2	680 (26.1%)	270 (25%)	
C	599 (23%)	203 (18.8%)	

## Two-year clinical outcomes by gender

	Male (N=1694)	Female (N=738)	P-value
Primary Safety Endpoint	222 (13.56%)	105 (14.72%)	0.9847
Clinically-driven TLR	150 (9.46%)	63 (9.23%)	0.7705
All death	214 (12.9%)	106 (14.64%)	0.6698
• Cardiac death	101 (6.28%)	55 (7.8%)	0.5879
Target vessel MI	118 (7.24%)	51 (7.23%)	0.5206
Definite or probable ST	34 (2.05%)	18 (2.53%)	0.5070
Definite ST	24 (1.45%)	10 (1.4%)	0.8537
• Acute	5 (0.3%)	3 (0.41%)	0.7481
• Subacute	5 (0.3%)	4 (0.55%)	0.2136
• Late	15 (0.92%)	2 (0.29%)	0.1685
• Very late	1 (0.07%)	1 (0.16%)	0.4340
Probable ST	10 (0.6%)	8 (1.13%)	0.4707
Clinical indicated TVR	169 (10.67%)	68 (9.99%)	0.6893
Any BARC Bleeding	372 (22.91%)	144 (20.28%)	0.2839
BARC Bleeding 2-5	292 (18.08%)	118 (16.58%)	0.6803
BARC Bleeding 3-5	138 (8.57%)	72 (10.23%)	0.1593

BARC, Bleeding Academic Research Consortium; MI, Myocardial infarction; ST, Stent Thrombosis; TLR, Target lesion revascularization; TVR, target vessel revascularization.

# What were the essential results?

- A total of 1694 (68.7%) men and 738 (31.3%) women were enrolled. Women were older with higher prevalence of acute coronary syndrome (31.4% vs. 25.2%) but lower prevalence of prior MI or revascularization and smoking.
- With respect to eligibility criteria, more women were  $\geq 75$  yrs of age, with higher prevalence of renal failure (24.1% vs. 16.9%) but men more often had an indication for oral anticoagulation (32.4% vs. 37.8%) and higher prevalence of malignancy, anticipated poor DAPT compliance or history of bleeding within the previous year.
- Angiographically, women had less multivessel disease, less severe stenosis, shorter lesion length and smaller reference vessel diameter. More than half of the patients underwent radial access PCI in both groups.

# What were the essential results?

## 2-year clinical outcomes by gender

	Men	Women	HR	p-value
Primary safety endpoint	13.6%	14.7%	1.11 (0.88-1.40)	0.3701
Cardiac death	6.3%	7.8%	1.28 (0.92-1.78)	0.1425
Target vessel MI	7.2%	7.2%	1.01 (0.73-1.40)	0.9530
Def/Prob ST	2.1%	2.5%	1.23 (0.70-2.18)	0.4745
TLR	9.6%	9.2%	0.96 (0.72-1.29)	0.7907
Major bleeding BARC 3 or 5	8.6%	10.2%	1.24 (0.93-1.65)	0.1412

# What were the essential results?

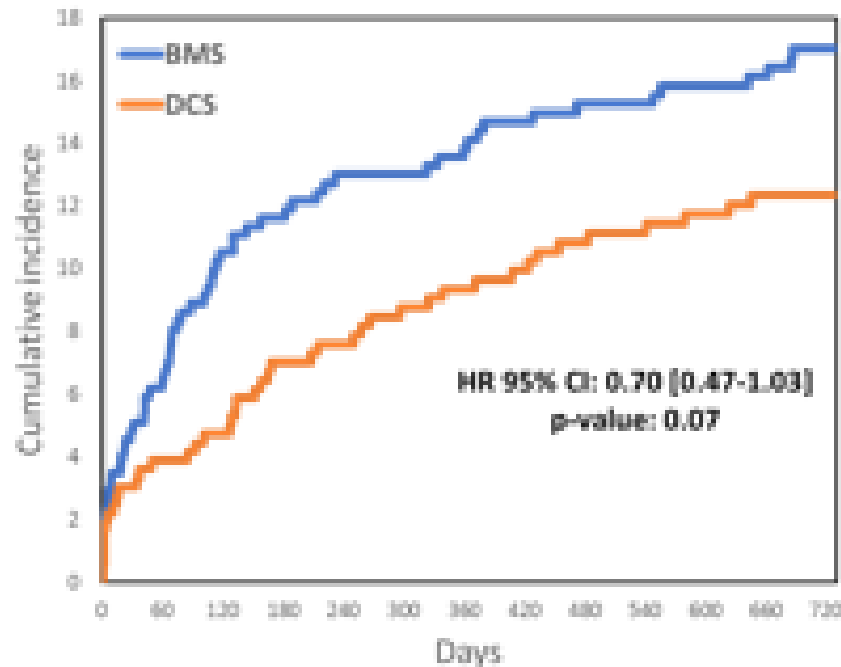
## 2-year clinical outcomes by stent type and gender

	Men		Women		
	Gazelle	BioFreedom	Gazelle	BioFreedom	p-interaction
Primary safety endpoint	14.5%	12.6%	17.0%	12.4%	0.4041
Cardiac death	6.4%	6.2%	8.0%	7.6%	0.9302
Target vessel MI	8.3%	6.2%	8.6%	5.8%	0.7288
Def/Prob ST	1.8%	2.3%	3.3%	1.7%	0.1345
TLR	12.0%	7.0%	12.1%	6.3%	0.6961
Major bleeding BARC 3 or 5	8.5%	8.6%	10.6%	9.8%	0.6697

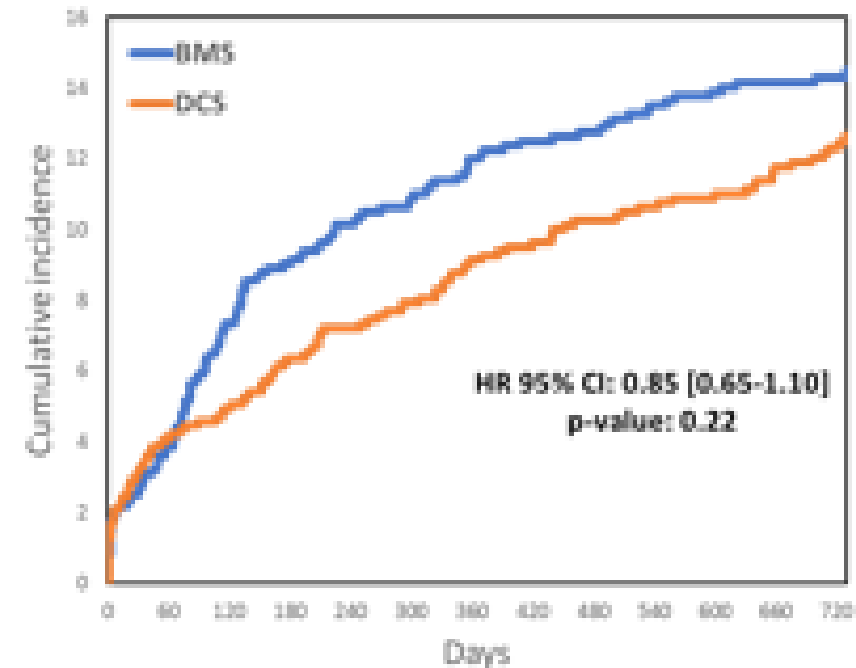
# Primary Endpoints by stent type and gender:

## Primary Safety Endpoint: Cardiac death, MI or stent thrombosis

### Females

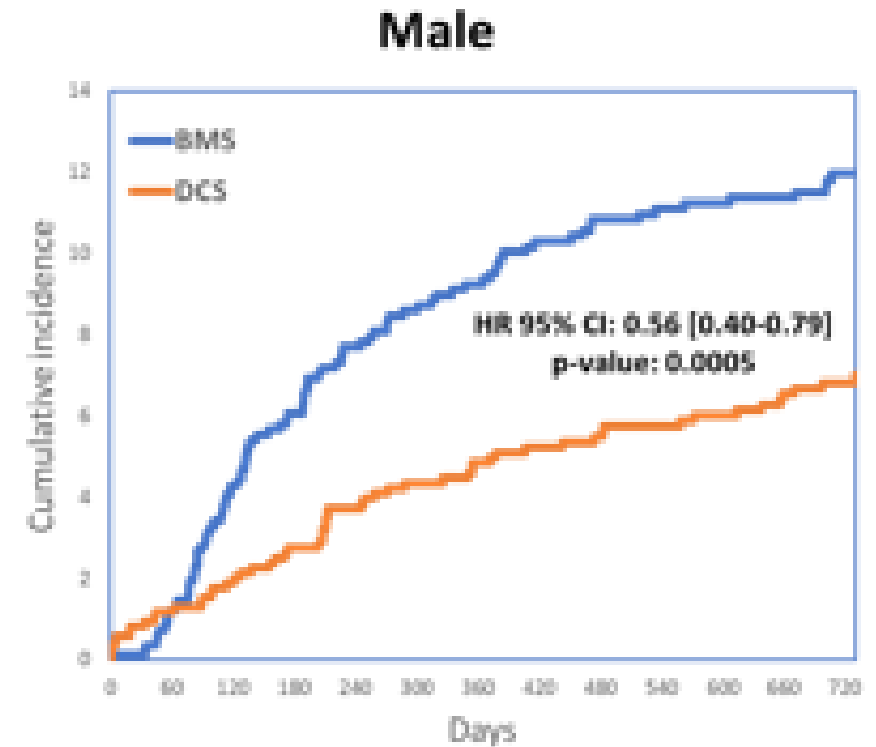
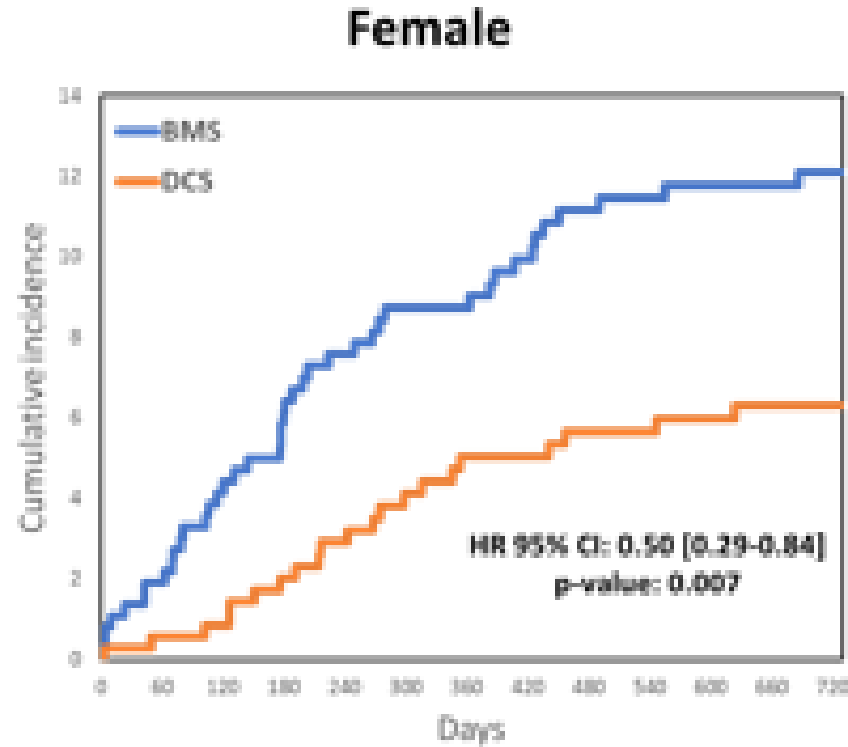


### Male - PSE



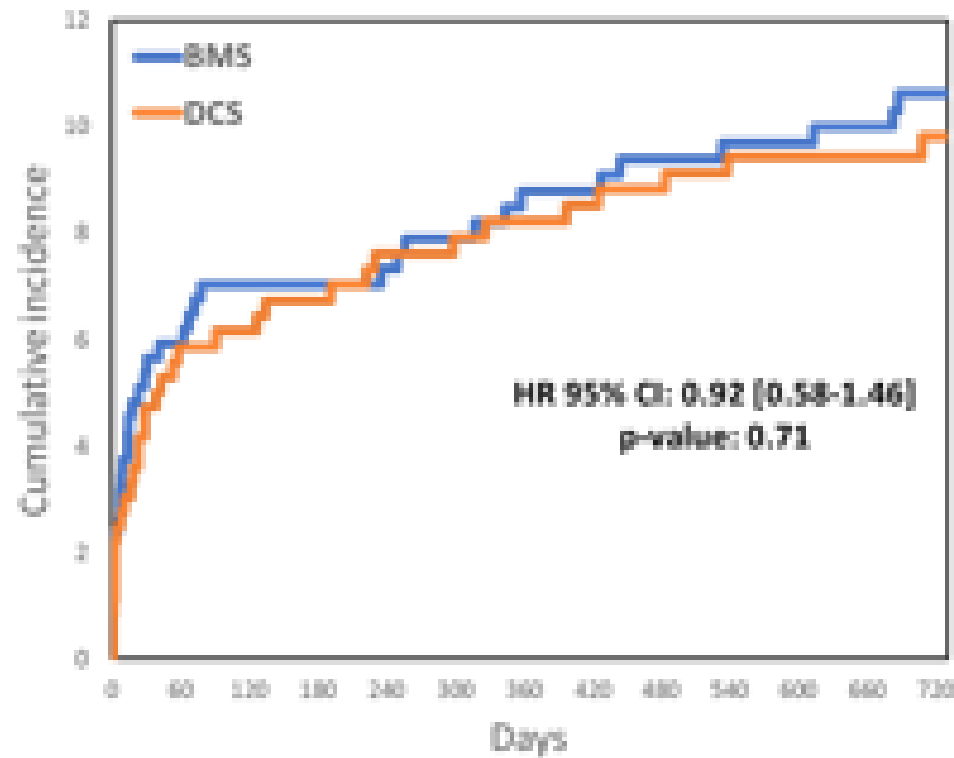
# Primary Endpoints by stent type and gender: **LEADERS**FREE

## Primary Efficacy Endpoint: Clinically driven TLR

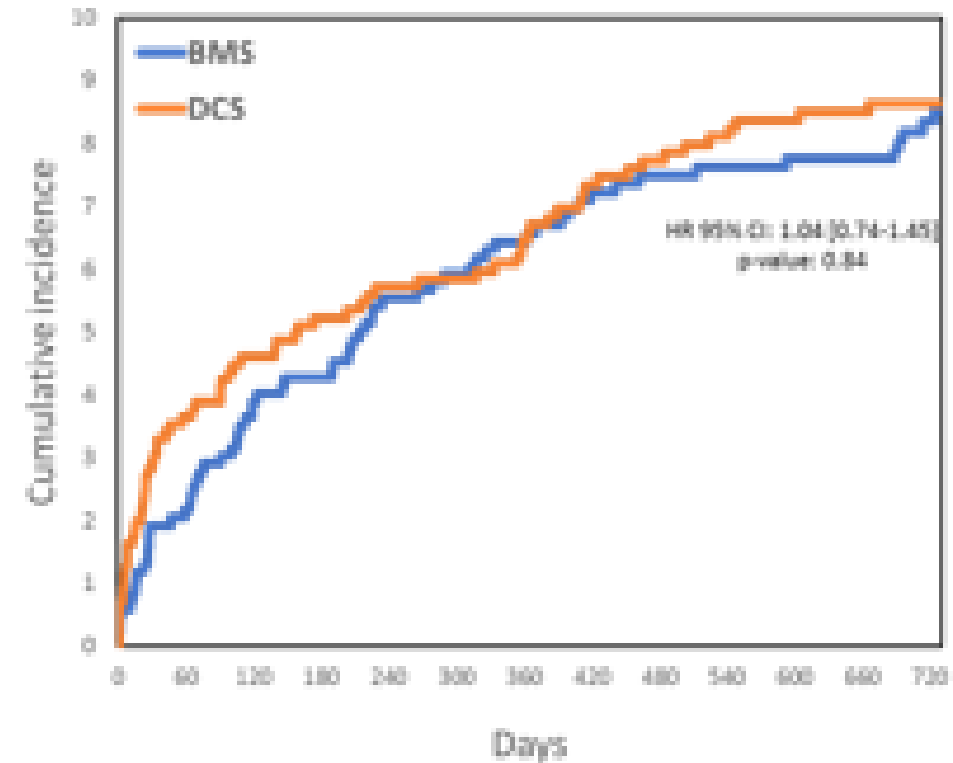


# Major bleeding BARC 3 or 5 by stent type and gender

## Female - BARC 3-5



## Male - BARC 3-5



## Why is it important?

- HBR women are more often older, present with renal failure and undergo PCI for ACS, whereas HBR men present with higher prevalence of malignancy, indication for oral anticoagulation and anticipated poor DAPT compliance within 12 months of PCI.
- Women had similar 2-year outcomes to men, suggesting that HBR women should not be denied benefits of PCI.
- In both groups polymer free DCS performed better than BMS in HBR patients with respect to TLR and should be favored regardless of gender.

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