

Drug-Eluting Stents vs. Bare Metal Stents In Saphenous Vein Graft Angioplasty (DIVA)



Emmanouil S. Brilakis, MD, PhD

*on behalf of the DIVA Trial Investigators and the Veterans Affairs
Cooperative Studies Program #571 Study Team, USA*



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Disclosures

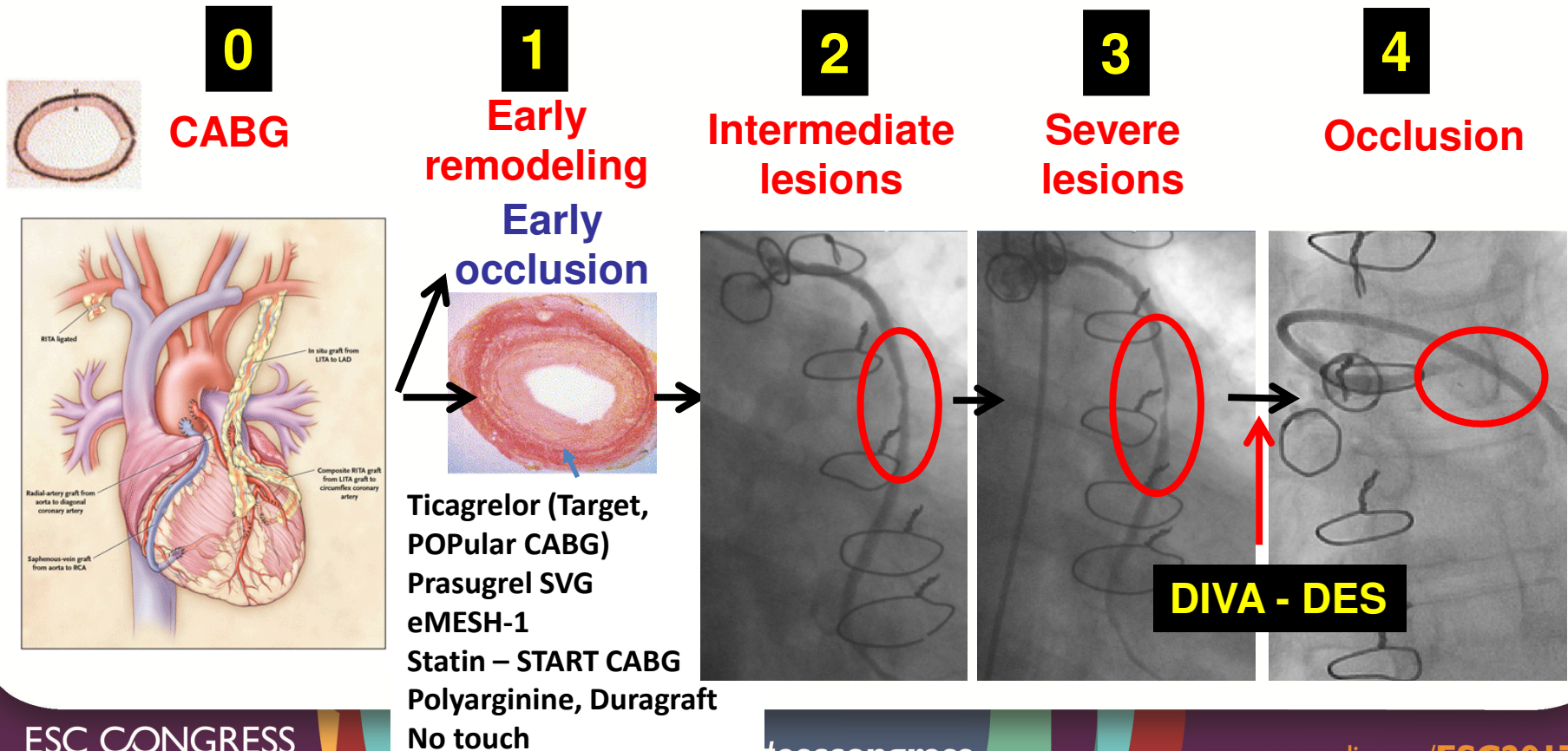
Consulting/speaker honoraria: Abbott Vascular, Amgen, Asahi, CSI, Elsevier, GE Healthcare, Medisure

Employment (spouse): Medtronic

Grants: Boston Scientific, Osprey

VA CSP#571 – DIVA

Natural history of SVGs



RCTs: DES vs. BMS in SVGs

Study	Year	N	Primary endpoint	DES event rate (%)	BMS event rate (%)	P
RRISC	2006	75	6-month angiographic restenosis	13.6	32.6	0.031
	2007		MACE at 32 months	58	41	0.13
SOS	2009	80	12-month angiographic restenosis	9	51	<0.001
	2010		Target vessel failure at 35 months	34	72	0.001
ISAR-CABG	2011	610	12-month composite of death, MI and TLR	15	22	0.02
BASKET-SAVAGE	2016	173	12-month composite of cardiac death, MI and TVR	2.3	17.9	<0.001



Limitations of prior RCTs

- **Small number of patients**
- **Unblinded**
- **Routine angiographic follow-up**
- **First generation DES**
- **Low use of embolic protection**

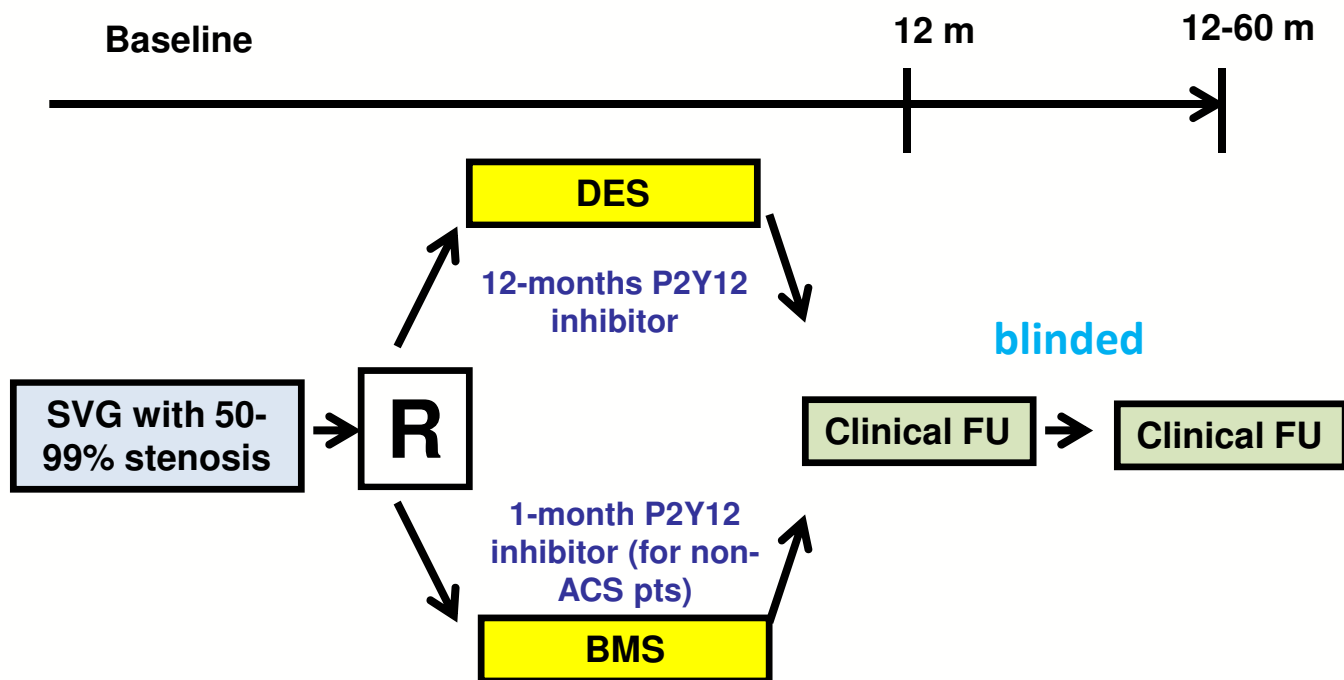
Study Design

- Prospective, double-blind, multicenter, randomized trial
- **Primary endpoint:** 12-month incidence of target vessel failure

(TVF: composite of cardiac death, target vessel myocardial infarction, or target vessel revascularization)



Study Design



Funding: Veterans Affairs Cooperative Studies Program

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Trial Leadership & Organization

PI/ Study Chair Co-Chair	Emmanouil S. Brilakis, MD, PhD Subhash Banerjee, MD
Sponsor	Veterans Affairs Cooperative Studies Program, United States Department of Veterans Affairs, USA
Executive Committee	Subhash Banerjee, MD; Deepak L. Bhatt, MD, MPH; Emmanouil S. Brilakis, MD, PhD; Todd Conner, PharmD (<i>Study Pharmacist</i>); Bob Edson, MA (<i>Study Biostatistician</i>); Steve Goldman, MD; David R. Holmes, MD; Bavana V. Rangan, BDS, MPH (<i>National Coordinator</i>); Sunil V. Rao, MD; Kendrick Shunk, MD, PhD; Beverly Ventura (<i>Project Manager</i>); Todd Wagner, PhD (<i>Health Economist</i>)
Steering Committee	Aaron R. Alsleben, ; Subhash Banerjee; Emmanouil S. Brilakis; Todd A. Conner; Bob Edson; Olinka Foster; Jeff Huminik, ; Alison Quien; Bavana V. Rangan; Lauren Uyeda ; Beverly Ventura; Todd Wagner; Scott Zellner; Nicholas Zemstov; Jerry Rogers

Trial Safety Oversight & Adjudication

DSMB	George Dangas, MD, PhD (Chair); Paul Heidenreich, MD; Motomi Mori, PhD; Srihari Naidu, MD; Paul Sorajja, MD; George Williams, PhD
Ex-Officio Members	Mei-Chiung Shih, PhD; Ying Lu, PhD
Clinical Events Committee	Imran Arif, MD; Jayant Bagai, MD; Crispin Davies, MD; Dmitriy Feldman, MD; Osvaldo Gigliotti, MD; Ion Jovin, MD; Nikolaos Kakouros, MBBS, PhD; Dharam Kumbhani, MD; Charles Lui, MD; Kartik Mani, MD; Calin Maniu, MD; Neelima Nadella, MD; William Penny, MD; Koushik Reddy, MD; Alan Schob, MD; Anjan Kumar Sinha, MD; Mladen Vidovich, MD
Angiographic and ECG Core Laboratory	Shuaib Abdullah MD; Judit Karacsonyi, MD; Peter Tajti, MD; Rahel Iwnetu, MD; Anna Kotsia, MD; Loren Makke RCIS; Michele Roesle RN



INCLUSION

1. Age $\geq$ 18 yrs
2. Planned PCI of 50-99% de novo SVG lesions (2.25-4.5 mm in diameter) causing ischemia
3. Intent to use EPD
4. Agree to participate and take prescribed medications
5. Informed consent

EXCLUSION

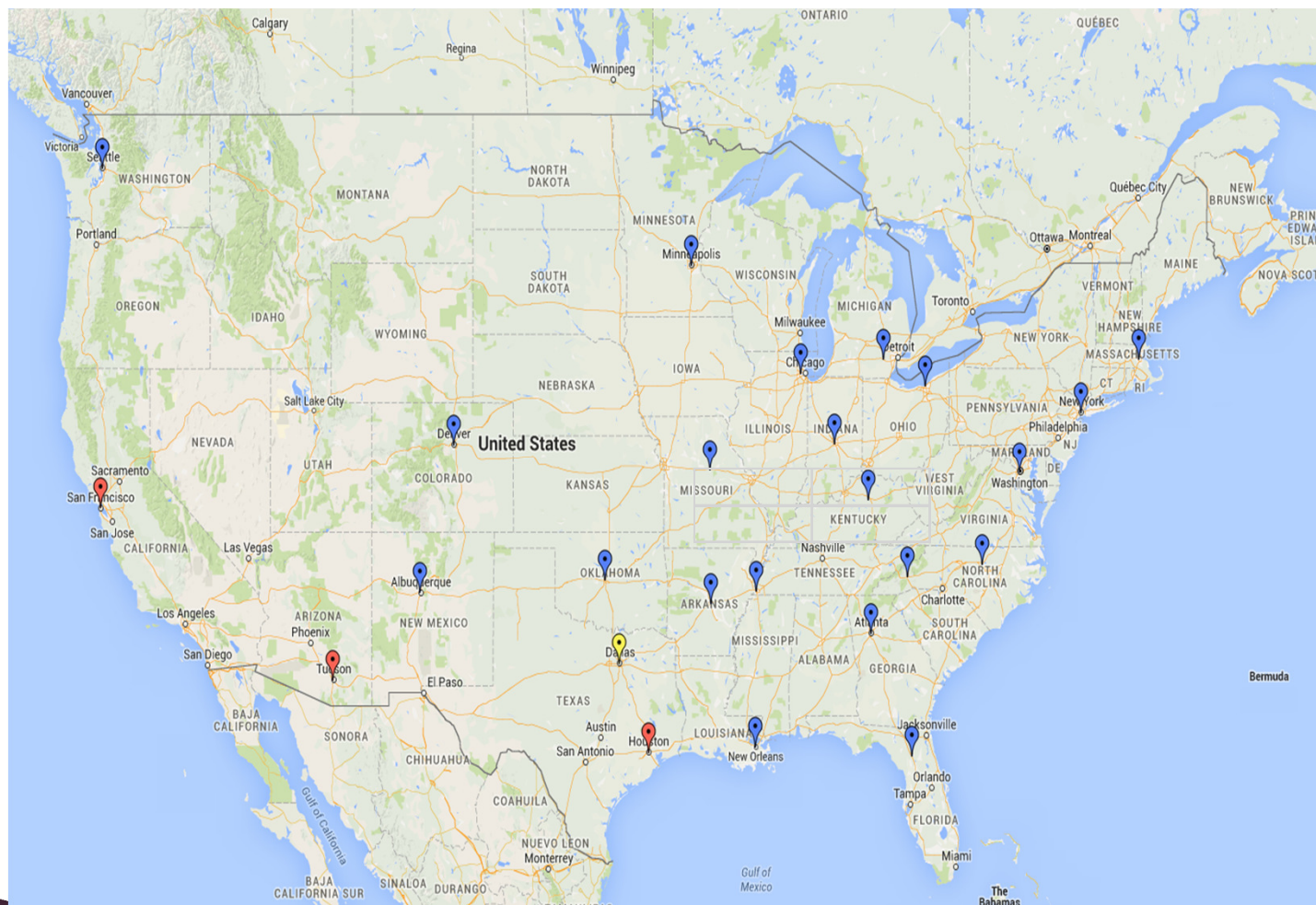
1. Planned non-cardiac surgery within 12 months
2. STEMI
3. Target SVG = last remaining vessel or left main equivalent
4. Any prior Rx of target lesion
5. Prior Rx of target vessel during past 12 months
6. Hemorrhagic diathesis or refuse transfusion
7. Warfarin required for 12 months + high risk for bleeding
8. +ve pregnancy test, breast-feeding or possible future pregnancy
9. Life expectancy < 12 months
10. History of allergic reaction to DES drug or metal
11. Allergy to clopidogrel in non-ACS pts
12. Participation in another RCT

Statistical design

- **Initial sample size:** 519 pts to achieve 90% power for the primary endpoint at 12 months FU assuming 12-month TVF rate 30% in BMS and 18% in DES
- **Interim analysis:** sample size increased to 762 due to lower than anticipated TVF rate
- **Enrollment stopped 12/31/2015:** 599 pts enrolled
 - 597 included in analysis due to improper consent in 2 pts

Power calculation

	HR	Events	Power
Original power estimation	0.556	123	90%
Power based on actual number of events in study	0.556	109	86%



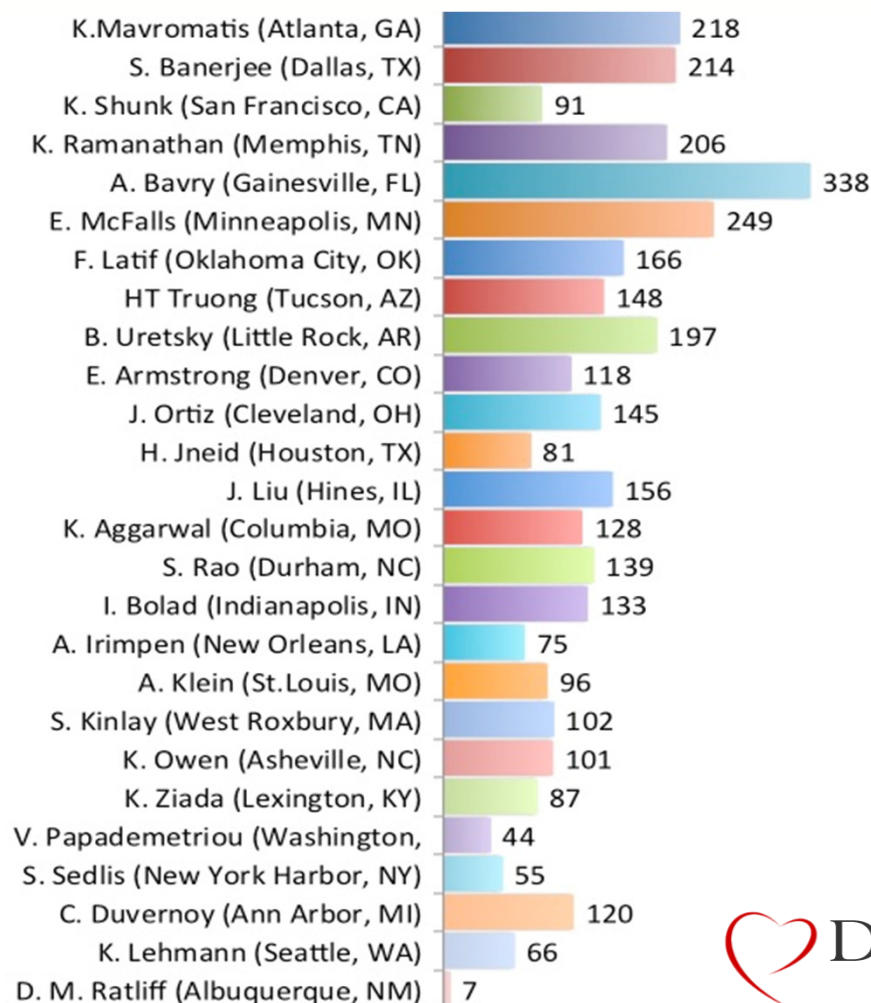
DIVA Study Sites

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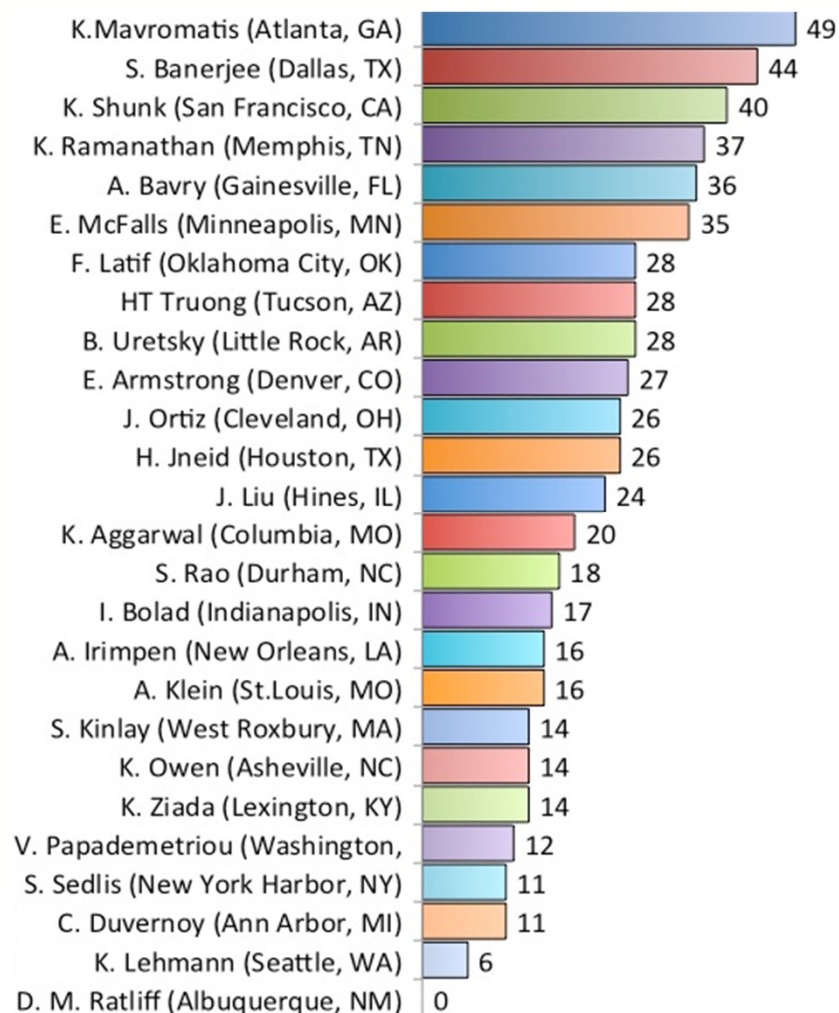
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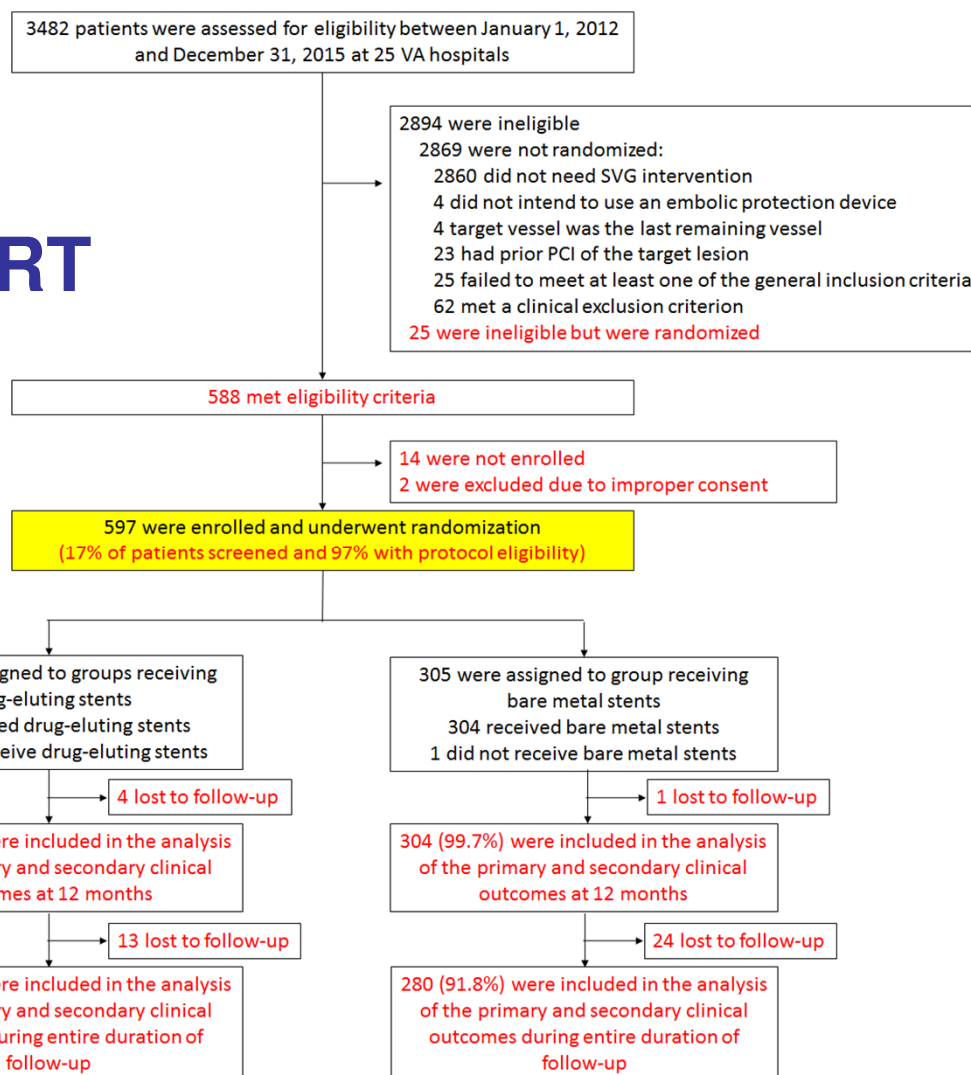
Total SCREENED= 3482



Total RANDOMIZED= 597



STUDY FLOWCHART



Patient Characteristics I

	DES (n = 292)	BMS (n = 305)	
Age – yrs	69.0 ± 7.4	68.2 ± 7.7	
Men, n (%)	290 (99%)	305 (100%)	
Race, n (%)			
White	263 (92%)	254 (86%)	
Black	17 (7%)	32 (12%)	
Body Mass Index (Kg/m²)	30.6 ± 5.6	30.4 ± 5.3	
Years since CABG	13.9 ± 6.7	12.8 ± 6.8	P=0.026

Patient Characteristics II

	DES (n = 292)	BMS (n = 305)
Presentation		
Stable angina	117 (40%)	105 (34%)
Unstable angina	89 (30%)	95 (31%)
Non-ST-segment elevation MI	66 (23%)	74 (24%)
Other	17 (6%)	30 (10%)
Hypertension, n (%)	278 (95%)	296 (97%)
Hyperlipidemia, n (%)	287 (98%)	294 (96%)
Diabetes mellitus, n (%)	173 (59%)	187 (61%)
Current smoking, n (%):	61 (21%)	72 (24%)
Prior MI, n (%)	163 (56%)	153 (50%)



Angiographic Characteristics I

	DES (n = 292)	BMS (n = 305)
SVG anastomosed to:		
LAD – diagonal n (%)	60 (21%)	73 (24%)
Circumflex – OM , n (%)	120 (41%)	125 (41%)
RCA - PDA, n (%)	112 (38%)	108 (35%)
SVG target lesion location		
Ostial, n (%)	68 (21%)	88 (25%)
Body, n (%)	234 (71%)	240 (67%)
Distal anastomosis, n (%)	28 (8%)	31 (9%)

Angiographic Characteristics II

	DES (n = 292)	BMS (n = 305)
Pre-stenting target SVG % diameter stenosis	82.7 ± 11.7	83.0 ± 11.2
Pre-stenting target SVG lesion flow		
0, n (%)	2 (1%)	3 (1%)
1, n (%)	10 (3%)	14 (4%)
2, n (%)	54 (16%)	42 (12%)
3, n (%)	264 (80%)	300 (84%)
Post-stenting target SVG % diameter stenosis	1.7 ± 9.9	1.1 ± 6.6
Post-stenting target SVG lesion flow		
0, n (%)	1 (0%)	1 (0%)
1, n (%)	1 (0%)	0 (0%)
2, n (%)	7 (2%)	4 (1%)
3, n (%)	321 (97%)	354 (99%)

Procedural Techniques

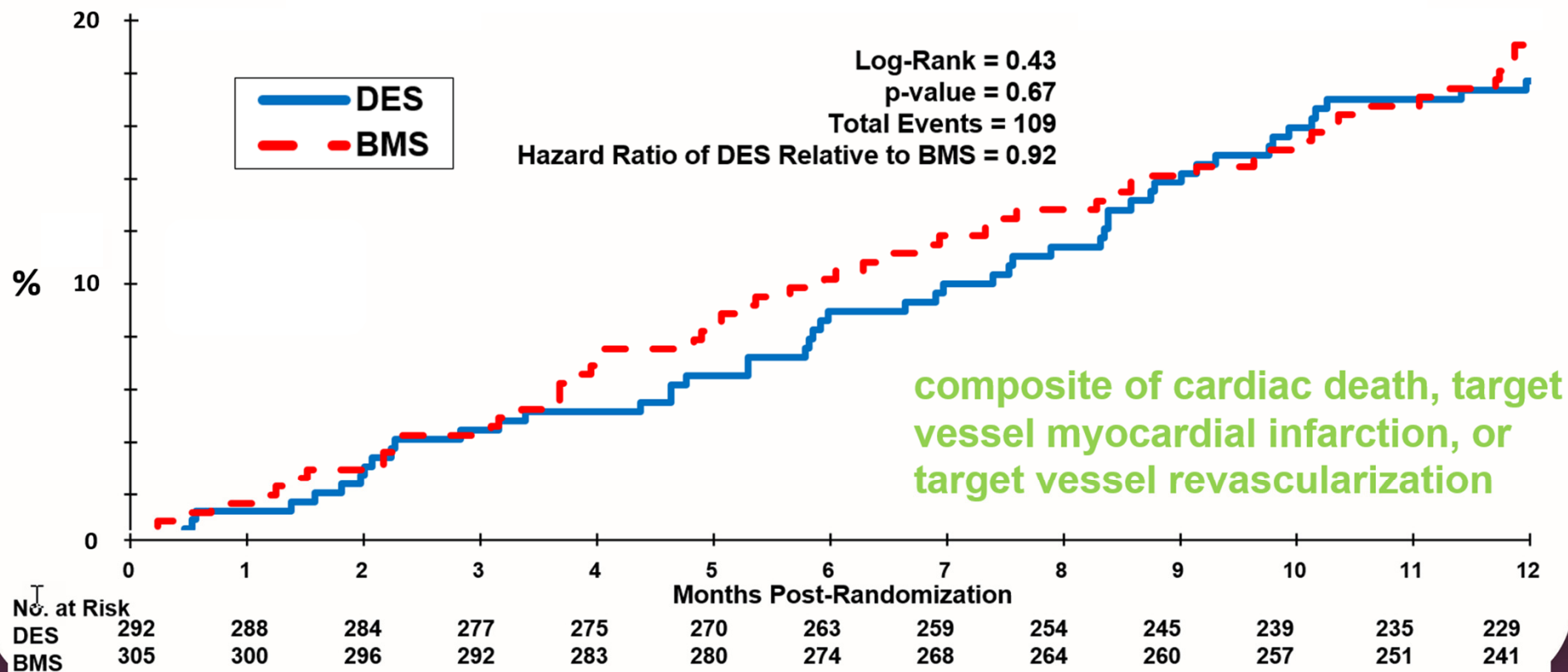
	DES (n = 292)	BMS (n = 305)
Anticoagulant		
Unfractionated heparin, n (%)	166 (57%)	177 (58%)
Bivalirudin, n (%)	123 (42%)	137 (45%)
Glycoprotein IIb/IIIa inhibitor , n (%)	44 (15%)	43 (14%)
Staged PCI, n (%)	30 (10%)	35 (12%)
Hemodynamic support during PCI, n (%)	1 (0%)	3 (1%)
Embolic protection device used, n (%)	199 (69%)	211 (69%)
Number of target SVGs intervened per patient	1.0 ± 0.2	1.0 ± 0.2
Number of target SVG lesions intervened per patient	1.2 ± 0.5	1.2 ± 0.5

Procedural Outcomes

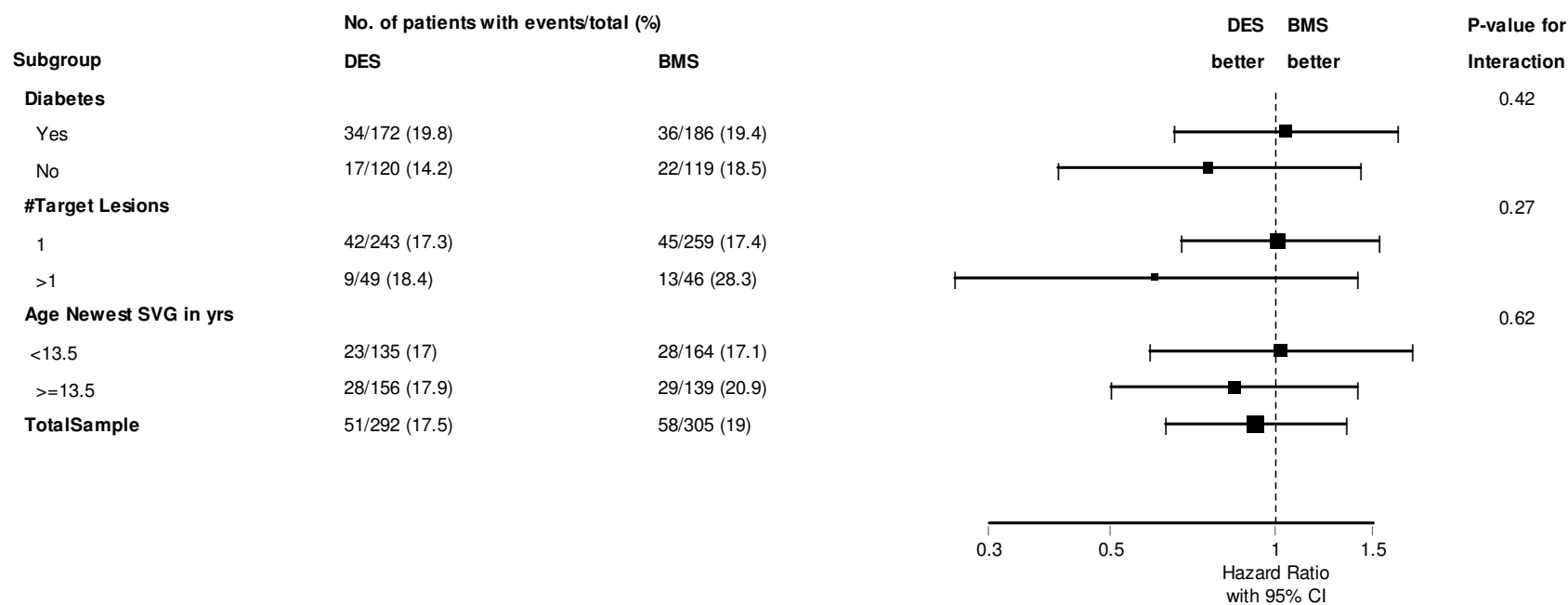
	DES (n = 292)	BMS (n = 305)
Number of stents in target SVG lesions per patient	1.3 ± 0.6	1.4 ± 0.8
Number of non-target lesions intervened per patient	1.4 ± 0.6	1.4 ± 0.7
Type of DES used in target lesions		
First generation, n (%)	17 (6%)	0 (0%)
Second generation, n (%)	261 (89%)	8 (3%)
Total length of stents in target lesion per patient (mm)	27.0 ± 18.9	26.6 ± 18.3
Target lesion stent diameter (mm)	3.37 ± 0.5	3.42 ± 0.56
Lesions with angiographic success, n (%)	274 (94%)	291 (95%)
Any procedural complication	15 (5%)	22 (7%)
Periprocedural MI	9 (3%)	23 (8%)

P=0.016

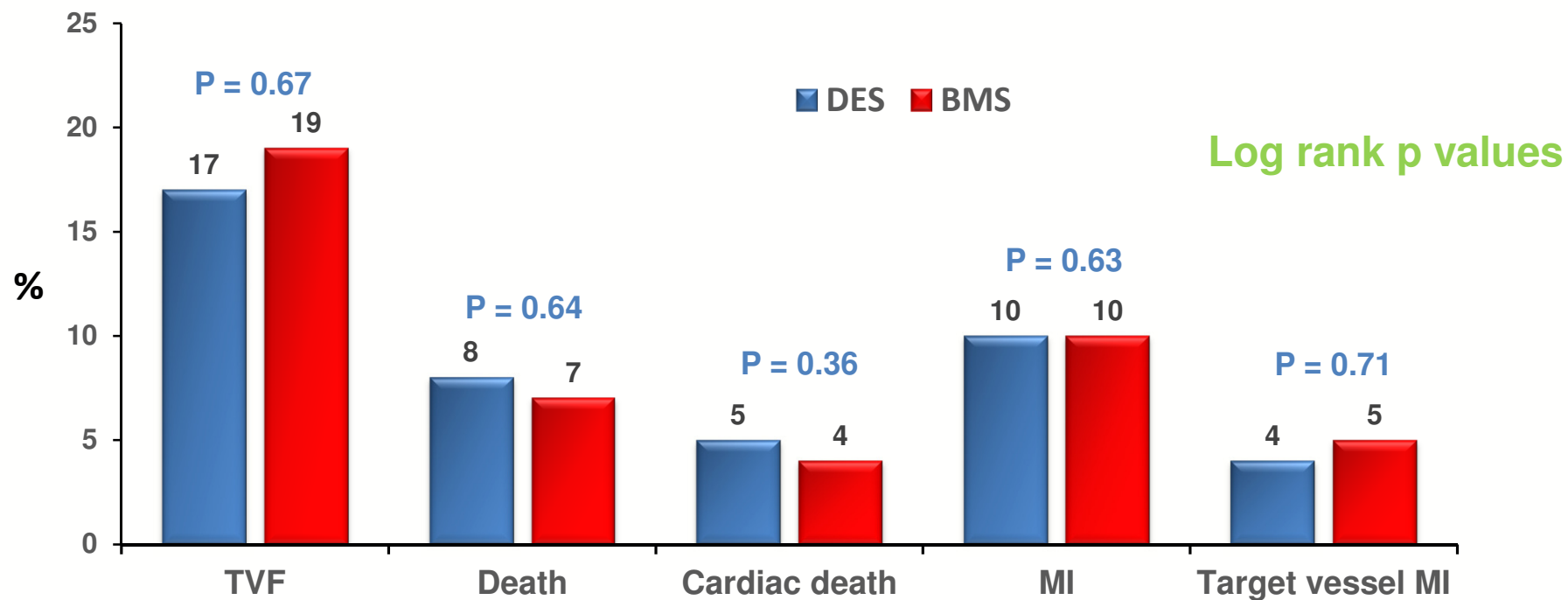
Primary endpoint: 12-month TVF



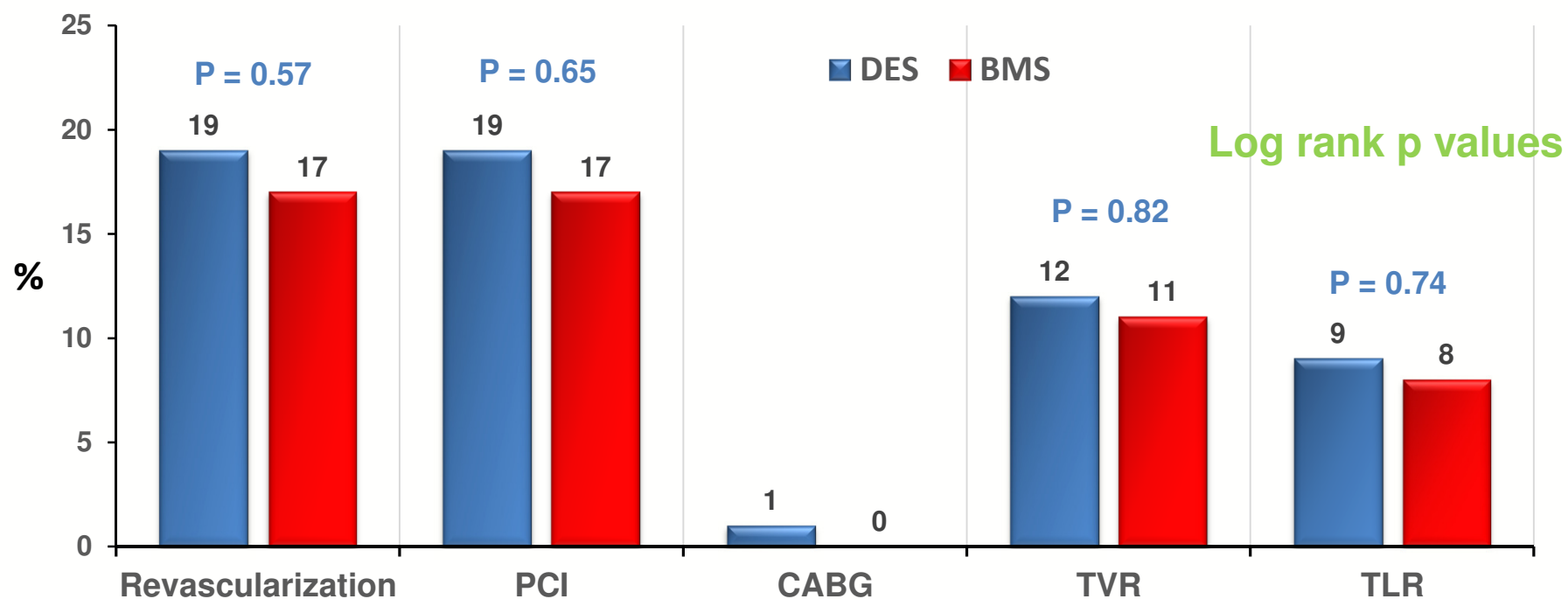
12-month primary endpoint: subgroups



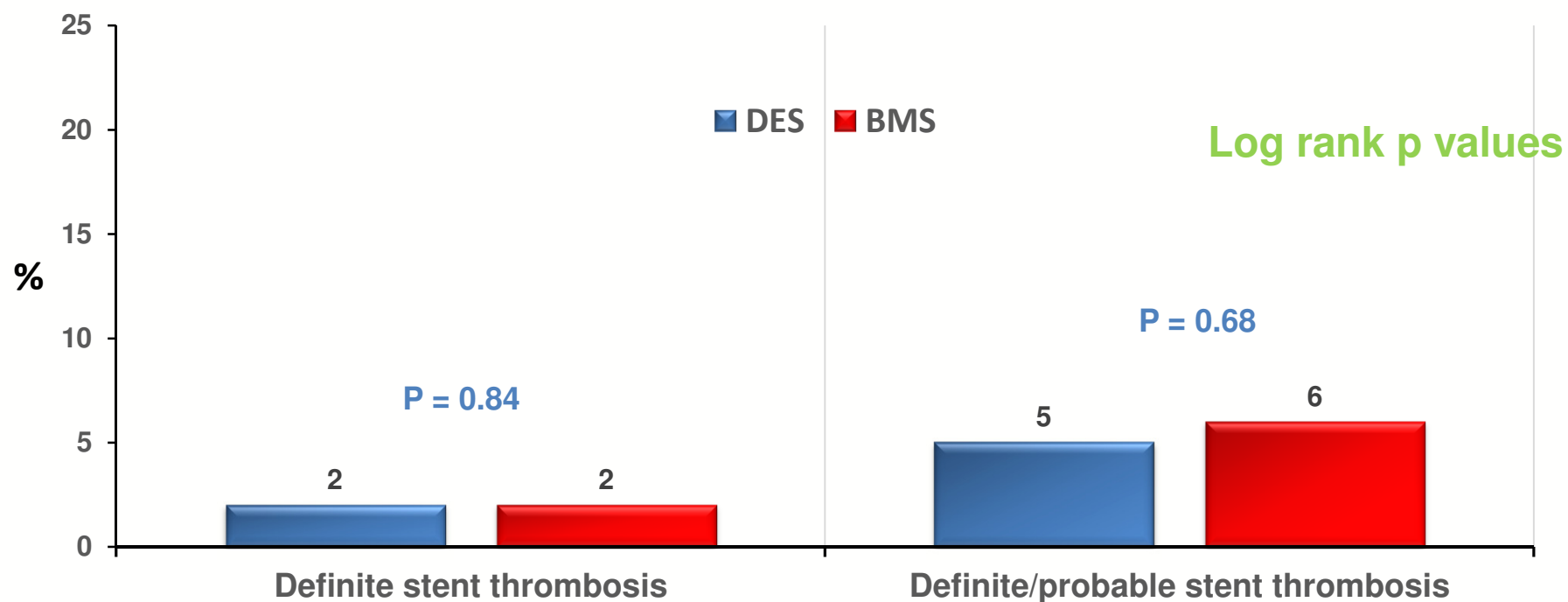
12-month Outcomes I



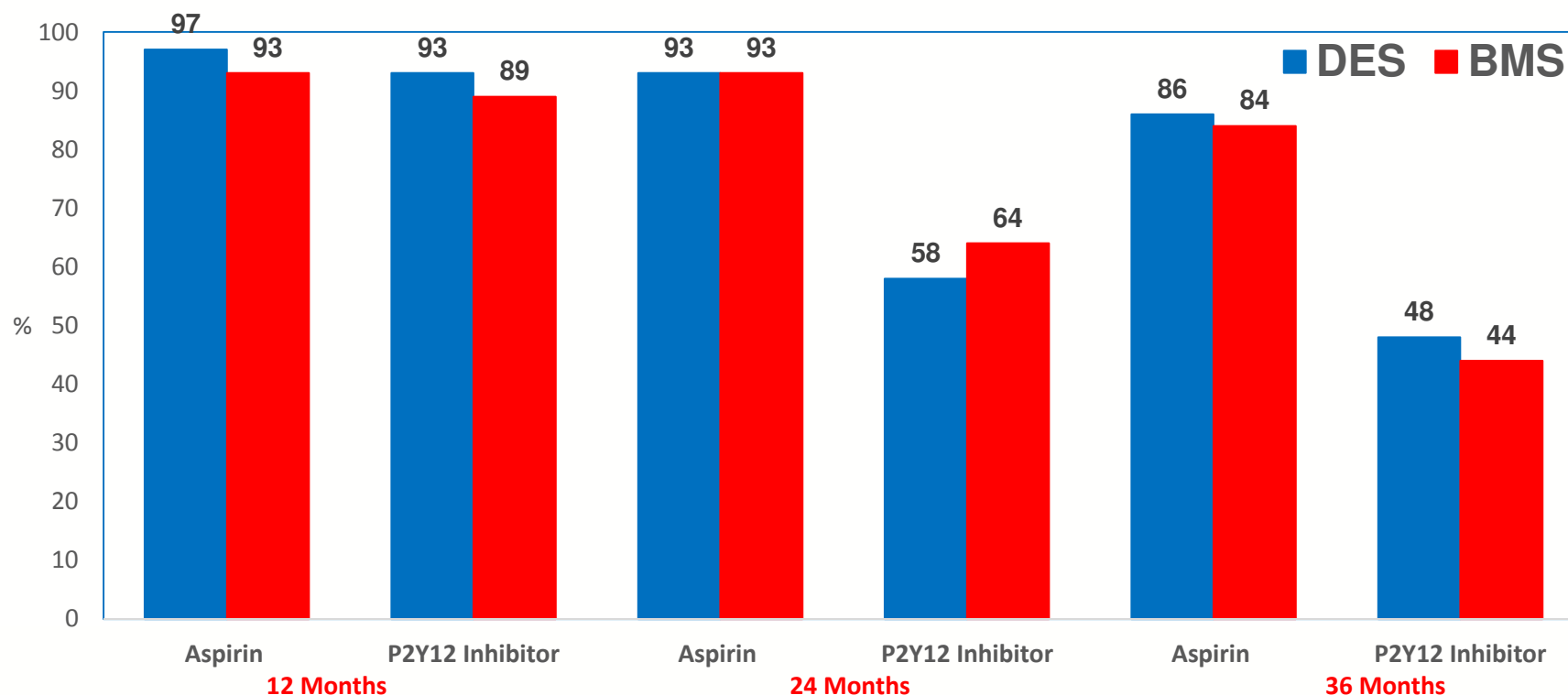
12-month Outcomes II



12-month outcomes III

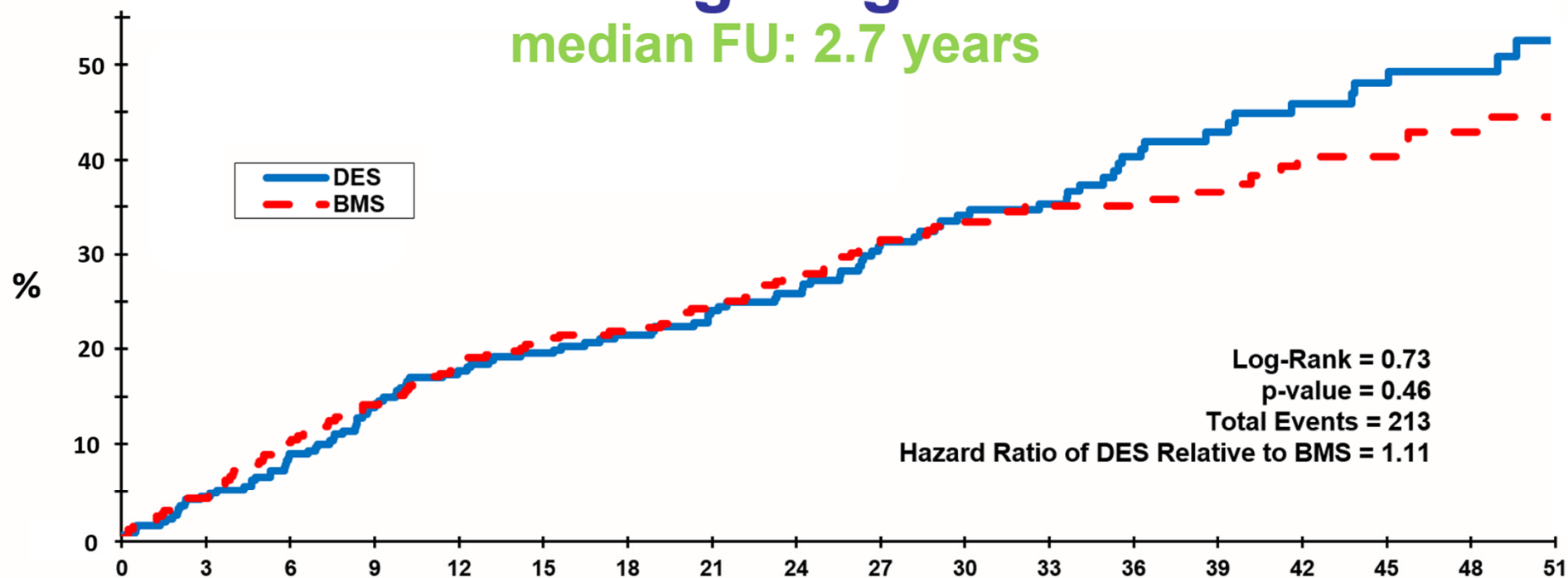


Antiplatelet medications during FU



TVF during long-term FU

median FU: 2.7 years

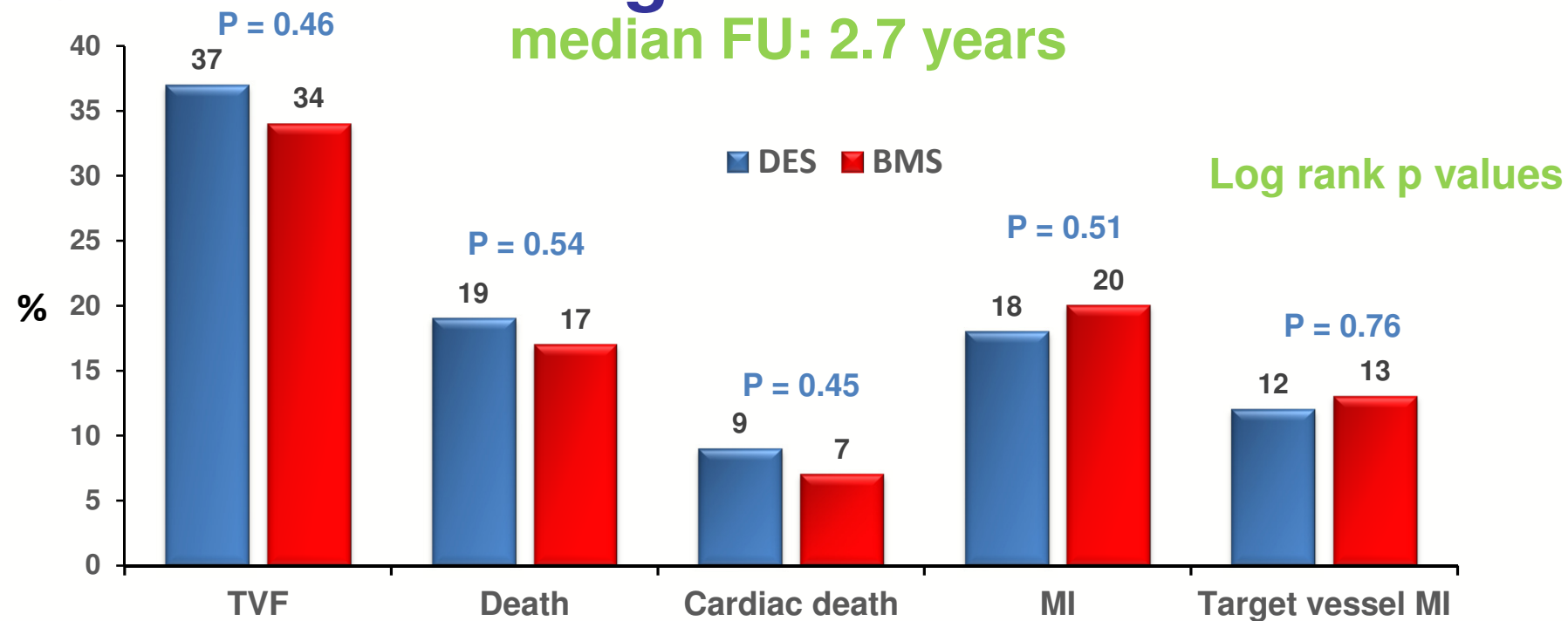


No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
DES	292	277	263	245	229	213	194	175	158	131	114	97	78	58	52	43	33	24
BMS	305	292	274	260	241	225	206	187	168	149	134	109	91	74	61	46	38	22



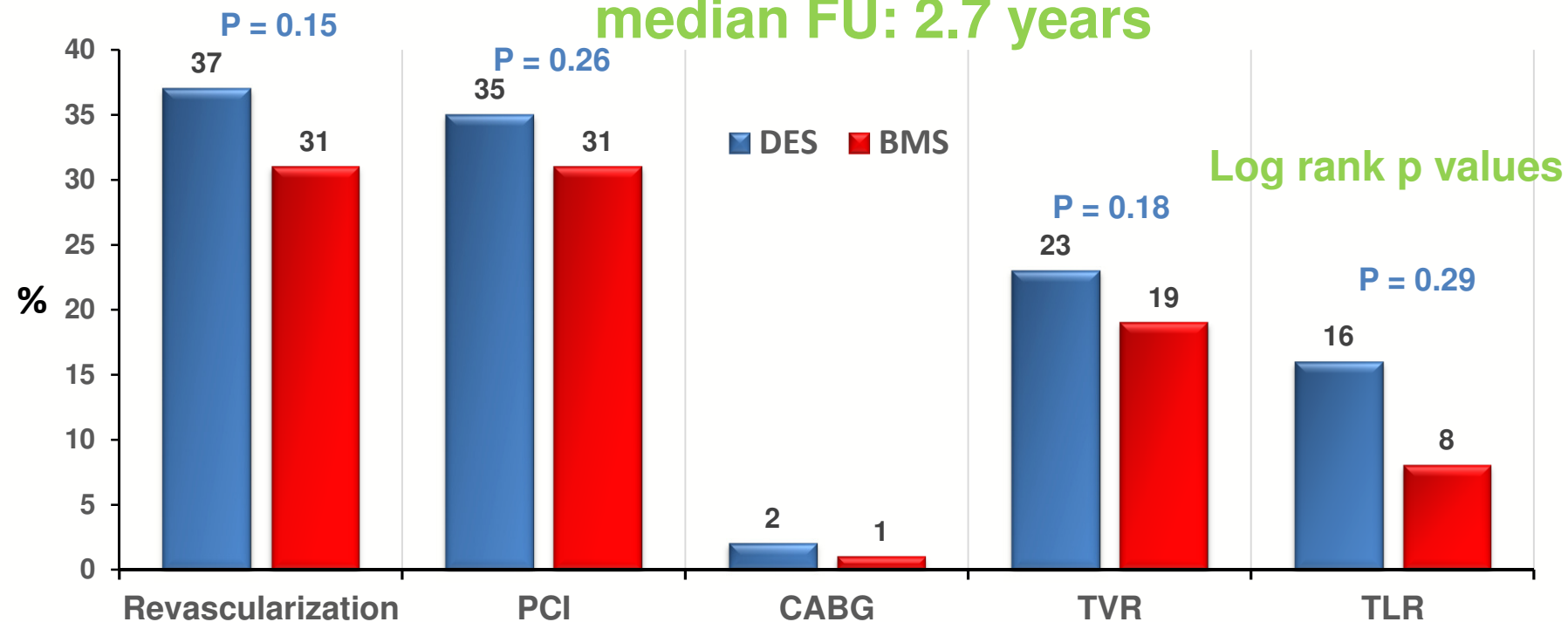
Long-term Outcomes I

median FU: 2.7 years



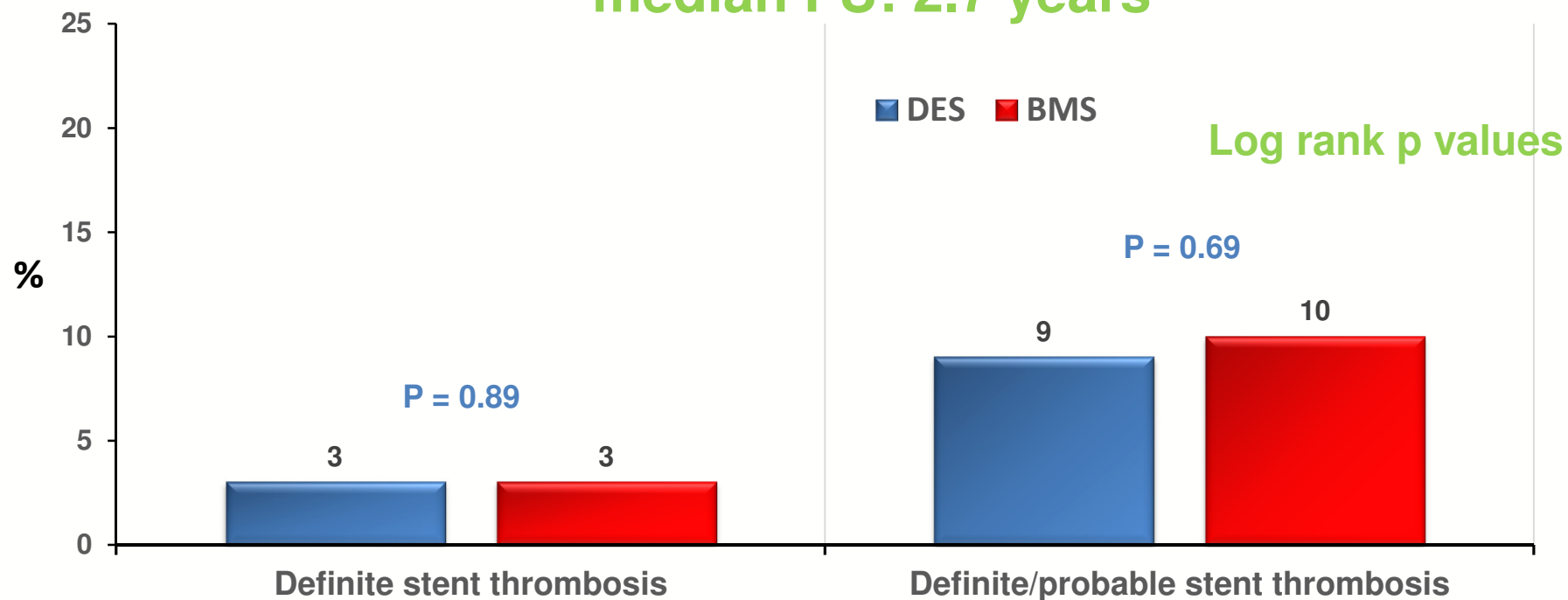
Long-term Outcomes II

median FU: 2.7 years



Long-term Outcomes III

median FU: 2.7 years



Limitations

- **Nearly all patients were men**
- **Study completed before reaching revised enrollment target, but still more patients than initially planned**

Conclusions

When stenting de novo SVG lesions:

- **No difference in short- and long-term outcomes between DES and BMS**
- **Novel strategies needed for treatment of severe SVG lesions**

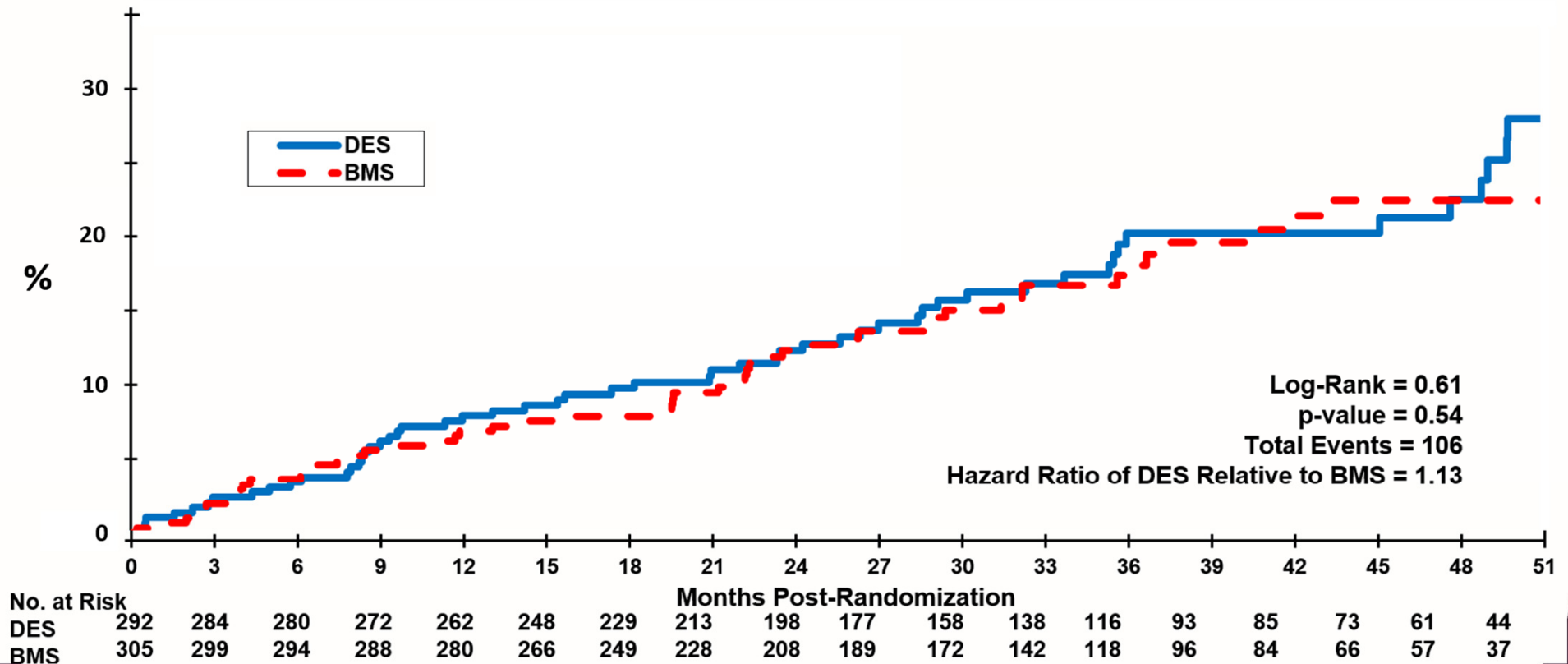
Backup slides

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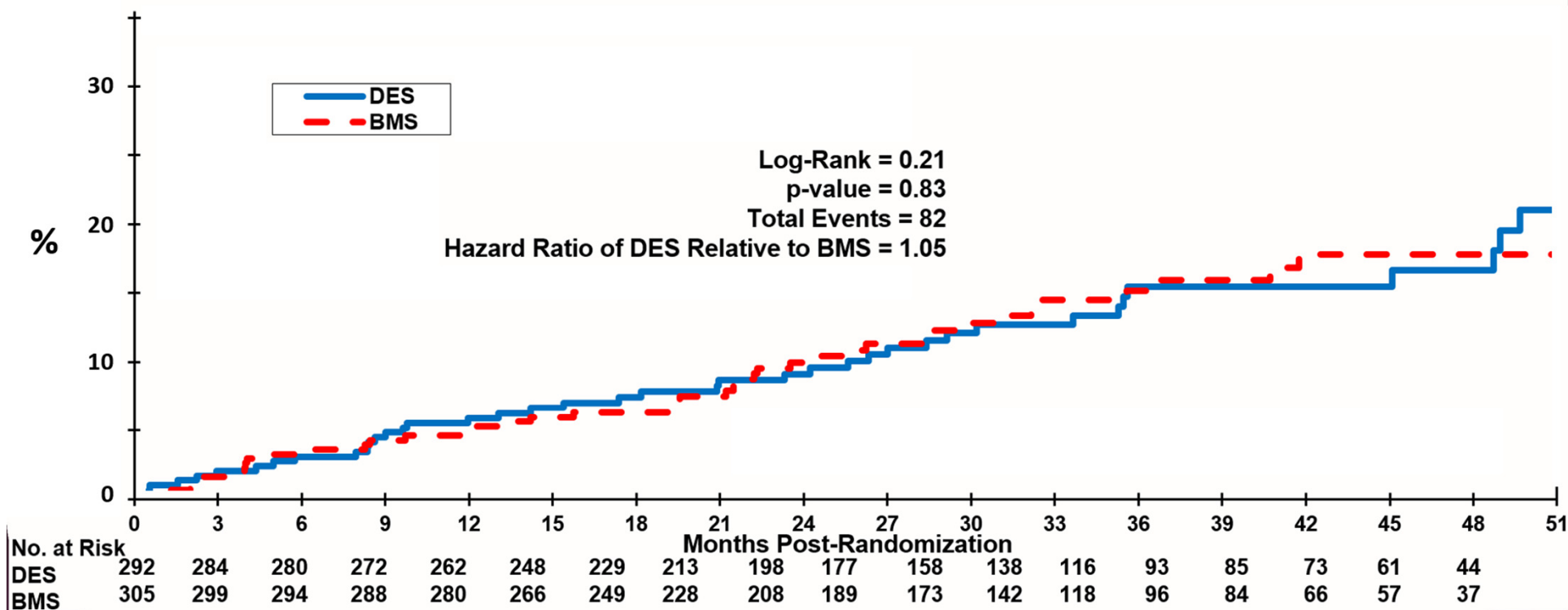
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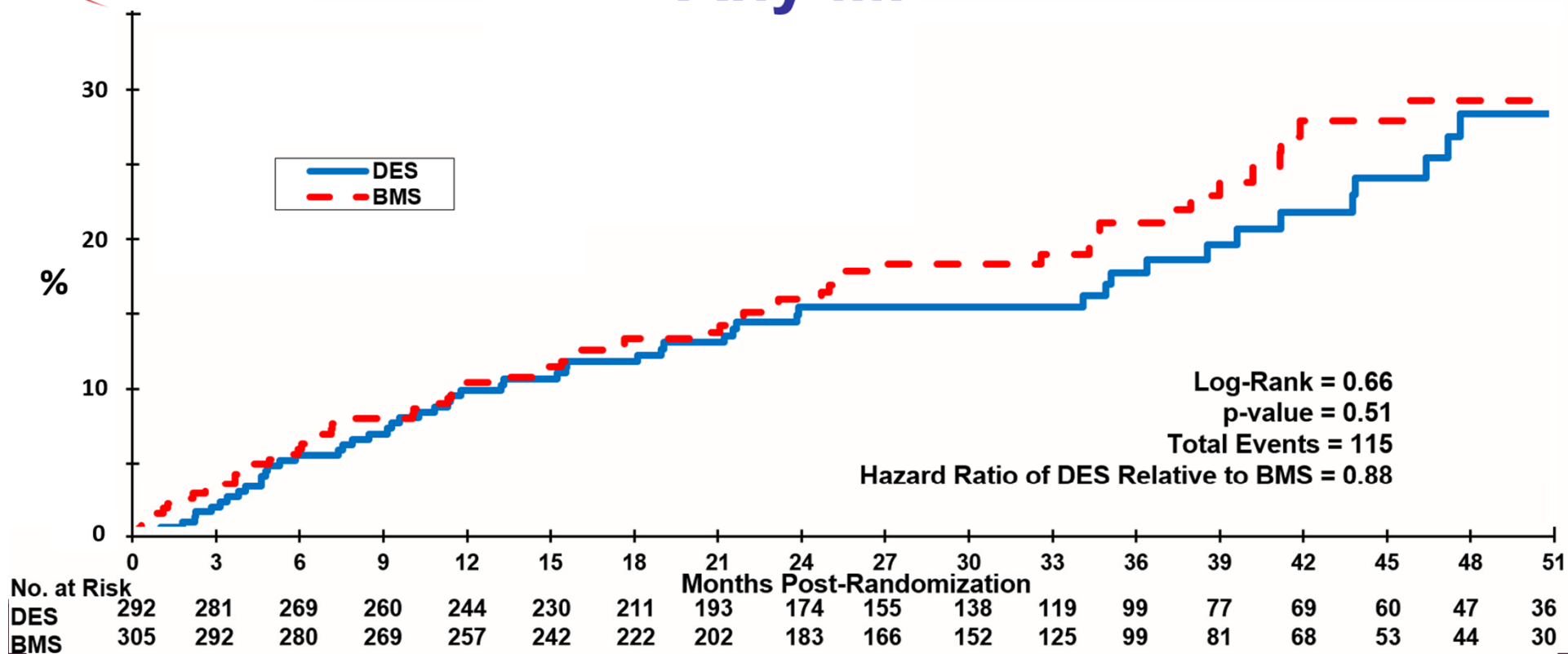
All cause death



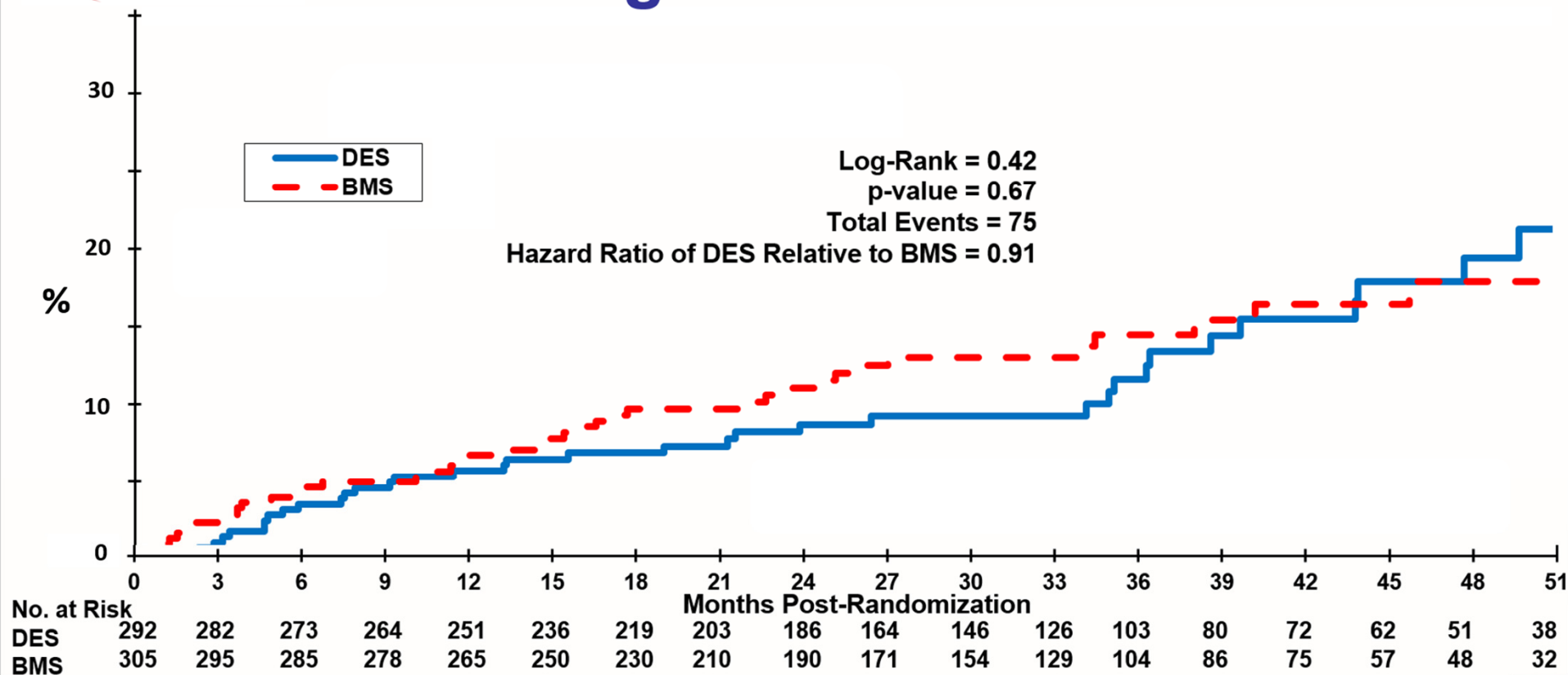
Cardiac death

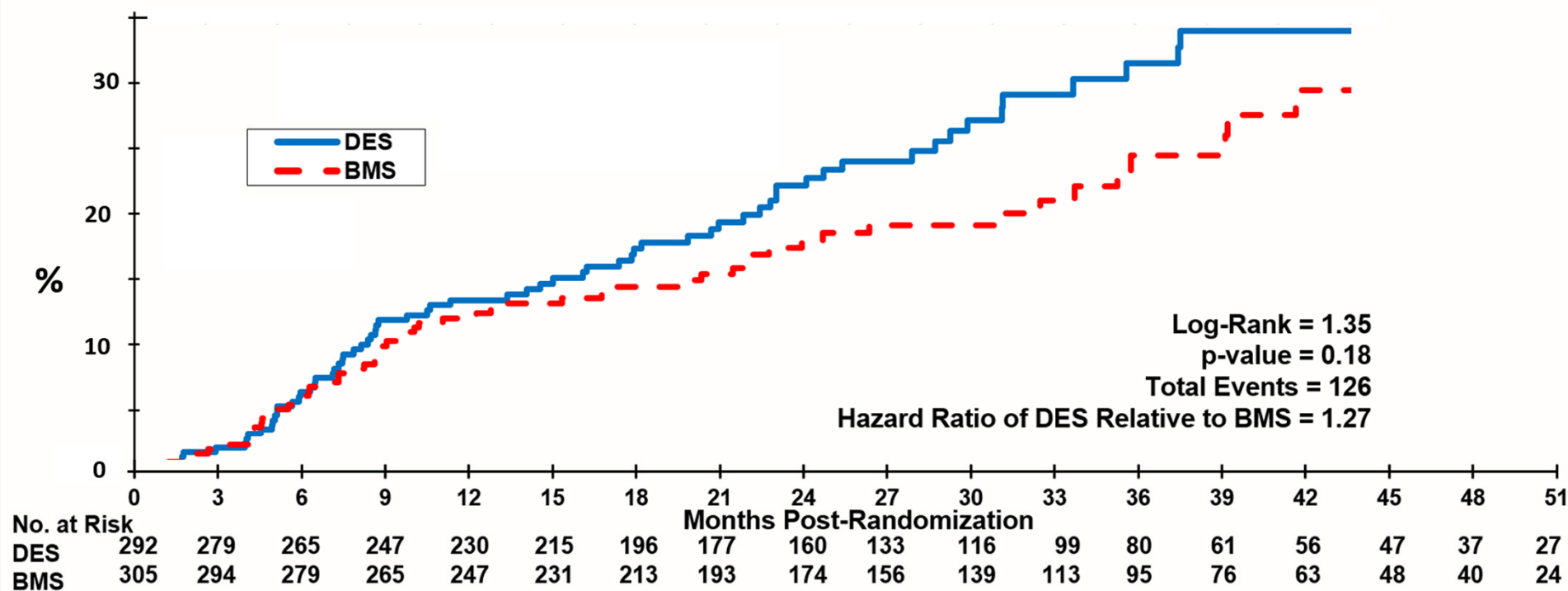


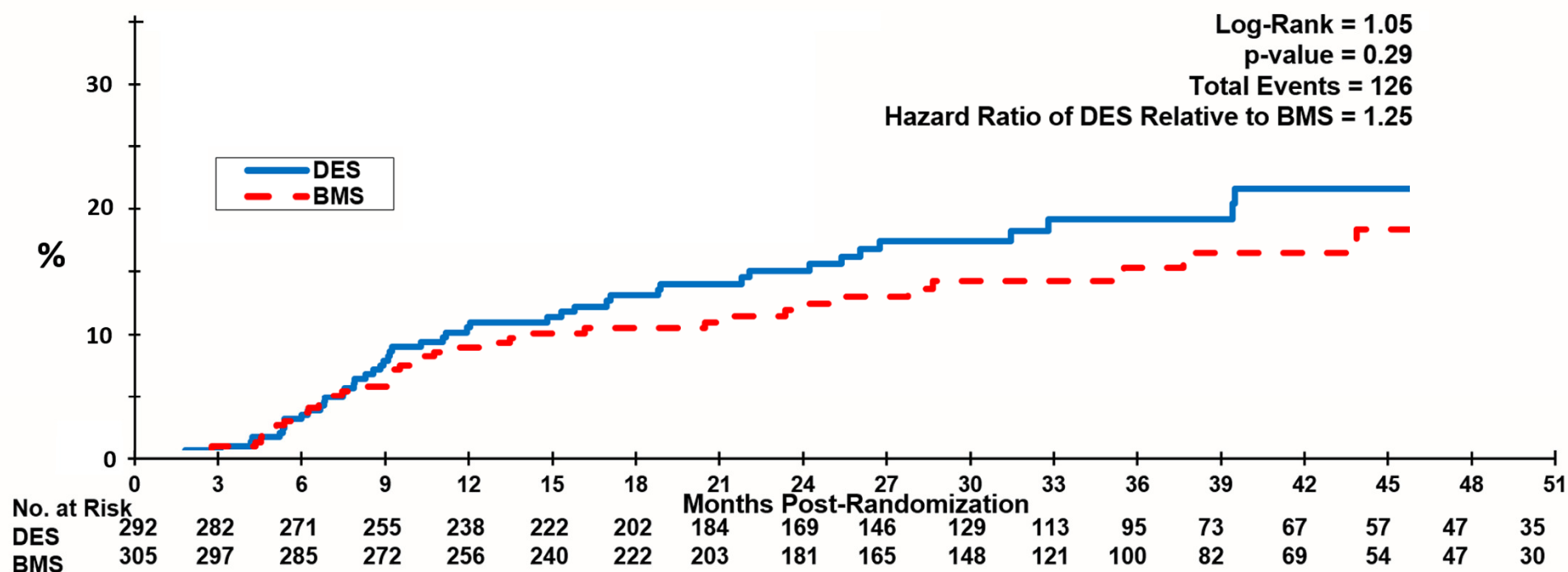
Any MI



Target vessel MI









Definite/probable stent thrombosis

