The MASTER II Trial

Comparison of the MGuard Embolic Protection Stent with Standard Stents in Acute Myocardial Infarction

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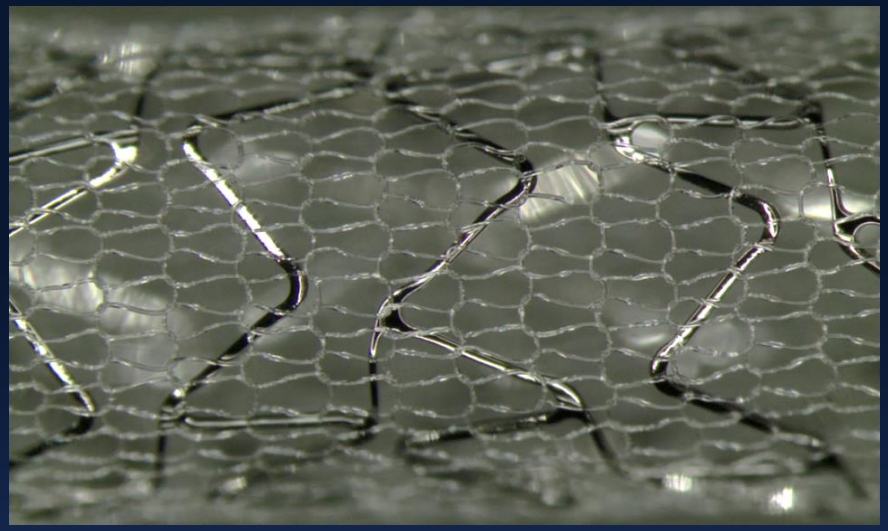
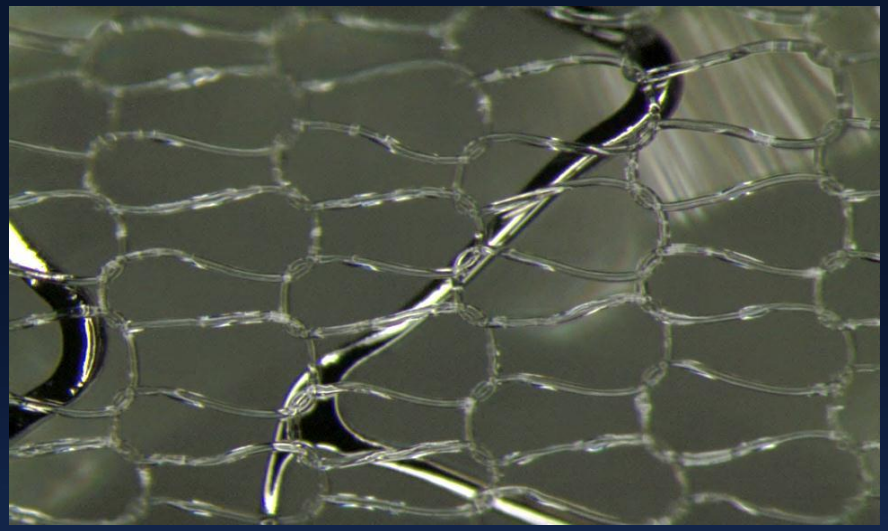
Background

- In the randomized MASTER I trial, among 433 pts with STEMI undergoing primary PCI, treatment with the MGuard stent compared to standard BMS/DES resulted in improved rates of TIMI-3 flow and ST-segment resolution, a trend toward lower mortality at 30-days and 1 year, but greater rates of restenosis and TLR
- The MASTER II trial was therefore designed as the US pivotal approval trial for the MGuard Prime embolic protection stent

The MGuard and MGuard Prime Embolic Protection Stent (EPS)





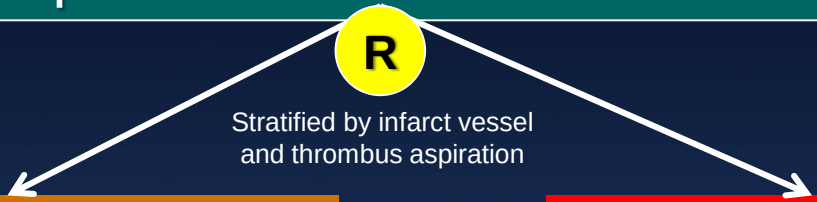
	MGuard	MGuard Prime
Metallic frame	316L stainless steel	L605 cobalt chromium
Strut width	100 µm	80 µm
Crossing profile	1.1 – 1.3 mm	1.0 – 1.2 mm
Shaft dimensions	0.65 – 0.86 mm	0.65 – 0.86 mm
Mesh sleeve	PET**	PET**
- Fiber width	20 µm	20 µm
- Net aperture size	150 - 180 µm	150 - 180 µm

*InspireMD, Tel Aviv, Israel; **Polyethyleneterephthalate

*M*GUARD for *A*cute *ST* *E*levation *R*eperfusion

The MASTER I Trial

STEMI with symptom onset within 12 hours at 433 pts at 50 sites in 9 countries



PCI with BMS or DES

PCI with MGuard

Follow-up: 30 days, 6 months, 1 year

Primary endpoint: ST-segment resolution at 60-90 minutes

Substudies:

Cardiac MRI: 60 pts (30 pts in each arm) at 3-5 days

Angio FU: 50 pts in MGuard arm at 13 months

Stone GW et al. J Am Coll Cardiol 2012;60:1975–84

MASTER I Results

Stone GW et al.
JACC 2012;60:1975–84

	MGuard stent (n=217)*	Control stent (n=216)**	*P* value
Device success†	95.9%	99.1%	0.03
TIMI-3 flow achieved	91.7%	82.9%	0.006
Angiographic success‡	91.7%	82.4%	0.004
Complete ST-segment resolution	57.8%	44.7%	0.008
Infarct size (%LV; n=59)	13.3 [7.9, 25.0]	16.6 [10.0, 22.6]	0.48
30-day events			
- Death	0%	1.9%	0.06
- MACE (CD, MI, ID-TLR)	1.8%	2.3%	0.75
1-year events	19 [15, 24]	20 [15, 24]	0.64
- Death	1.0%	3.3%	0.09
- TLR	8.6%	0.9%	0.0003
- MACE (CD, MI, ID-TLR)	9.1%	3.3%	0.02
- Stent thrombosis (def/prob)	2.3%	0.9%	0.26

*191 (88%) MGuard, 26 MGuard Prime; **39.8% DES; †<50% final residual stenosis using only the randomized stent; ‡< 50% final residual stenosis and TIMI-3 flow

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*M*GUARD for *A*cute *ST* *E*levation *R*eperfusion II

The MASTER II Trial

STEMI with symptom onset within 12 hours
- 1,114 pts at 70 sites in 11 countries -

R

Stratified by LAD vs. non-LAD infarct vessel and intended DES vs BMS

PCI with BMS or DES

PCI with MGuard Prime

Follow-up: 30 days, 6 months, 1 year, 2 years, 3 years

1° efficacy endpoint: ST-segment resolution at 60-90 minutes (Sup)
1° safety endpoint: Death or reinfarction at 365 days (NI)

2° efficacy endpoint: Infarct size day 3-7 MRI (n=352 P/MLAD) (Sup)
2° safety endpoint: In-stent late loss 12 months (n=200 BMS strata, NI)

MASTER II
Principal Inclusion Criteria

- Symptoms consistent with STEMI between 30 mins and 12 hrs of symptom onset
- ≥2 mm of ST-segment elevation in ≥2 contiguous leads
- TIMI 2 or 3 flow restored either spontaneously, by aspiration or pre-dilatation
- PCI of a single de novo lesion with RVD ≥2.75 to ≤4.0 mm and length ≤24 mm (capable of being covered by a single study stent)

MASTER II
Principal Exclusion Criteria

- LBBB, paced rhythm, etc.
- Prior PCI w/i 30d or planned non-TV PCI w/i 7d or planned TV-PCI w/i 12 months
- Cardiogenic shock or CPR
- ≥50% left main stenosis present
- Infarct lesion ostial or bifurcation with ≥2.0 mm sidebranch
- Target vessel or infarct lesion excessively tortuous, angulated or with moderate to heavy calcification
- Prior stent within target vessel

MASTER II Study Organization

Principal investigator:	Gregg W. Stone
Co-principal investigator:	Jose PS Henriques
Steering committee:	Gregg W. Stone, Jose PS Henriques, Eli Bar, Donald Cutlip, Ori Ben-Yehuda
Data monitoring:	Medpace Medical Device, Minneapolis, MN, USA; MEDPASS, Paris, France and KCRI, Krakow , Poland
Data management and analysis:	Cardiovascular Research Foundation (CRF), NY, NY; Ori Ben-Yehuda (Director), Melissa Nichols
Event adjudication:	CRF; Sorin Brener (Director), Alejandra Guerchicoff (Co-director)
ECG core laboratory:	CRF; Jose Dizon (Director)
Angio core laboratory:	CRF; Philippe Genereux (Director)
MRI core laboratory:	CRF; Steve Wolff (Director), Akiko Maehara, (Co-director)
DSMB:	Bernard Gersh (Chair), David Faxon, Stuart Pocock
Sponsor and funding:	InspireMD, Tel Aviv, Israel

MASTER II **Enrollment**

1. Enrollment was voluntarily suspended on April 30th, 2014 after 310 patients had been randomized at 46 international sites because of a higher than expected rate of stent dislodgement with the MGuard Prime

2. No patient in MASTER II experienced an endpoint event due to a stent dislodgement

3. The issue has been addressed with a manufacturing change; device re-approval has been granted in US for IDE and EU for commercial use

4. Sponsor elected to terminate enrollment because of slow recruitment in the BMS strata, especially in US

MASTER II Top 12 Enrolling Sites

Between July 25th, 2013 and April 29th, 2014,
310 pts were randomized at 46 sites in 12 countries

1. Peep Laanmets, North Estonia Regional Hospital, Tallinn, Estonia	22
2. Andreas Baumbach, Bristol Heart Institute, Bristol, UK	21
3. Marek Kondys, III Oddzial Kardiologii, Dabrowa Gornicza, Poland	20
4. Niels van Royen, VUMC Amsterdam, Amsterdam, Netherlands	16
5. Martin Mates, Na Homolce Hospital, Prague, Czech Republic	15
6. Jan Peruga, Medical University, Lodz, Poland	14
7. Aleksander Zurakowski, American Heart of Poland, Chrzanow, Poland	13
8. Giovanni Amoroso, Onze Lieve Vrouwe Gasthuis, Amsterdam, NL	12
9. Jose P.S. Henriques, Academic Medical Center, Amsterdam, NL	11
10. Adam Witkowski, Institute of Cardiology, Warszaw, Poland	11
11. Christopher Malkin, Leeds General Infirmary, Leeds, UK	11
12. Jan Pattanayak, Asheville Cardiology Associates, Asheville, NC, US	10

MASTER II Baseline Characteristics

	MGuard Prime (n=155)		Control stent (n=155)
Age (years)	60 [52, 66]	*	62 [55, 70]
Male	79.4%		73.5%
Hypertension	40.6%		49.7%
Hyperlipidemia	31.6%		28.4%
Diabetes mellitus	13.5%		18.1%
Cigarette smoking	52.3%		45.5%
Prior MI	7.1%		6.5%
Prior PCI	7.1%		5.2%
Symptoms to device, mins	172 [130, 322]		170 [122, 253]
Infarct artery = LAD	36.8%		37.4%
Baseline TIMI flow = 0/1**	67.8%		71.6%
Baseline RVD, mm**	3.03 [2.73, 3.31]		2.97 [2.68, 3.35]
Baseline DS %**	100.0 [83.8, 100.0]		100.0 [85.1, 100.0]

*P=0.04; **core lab

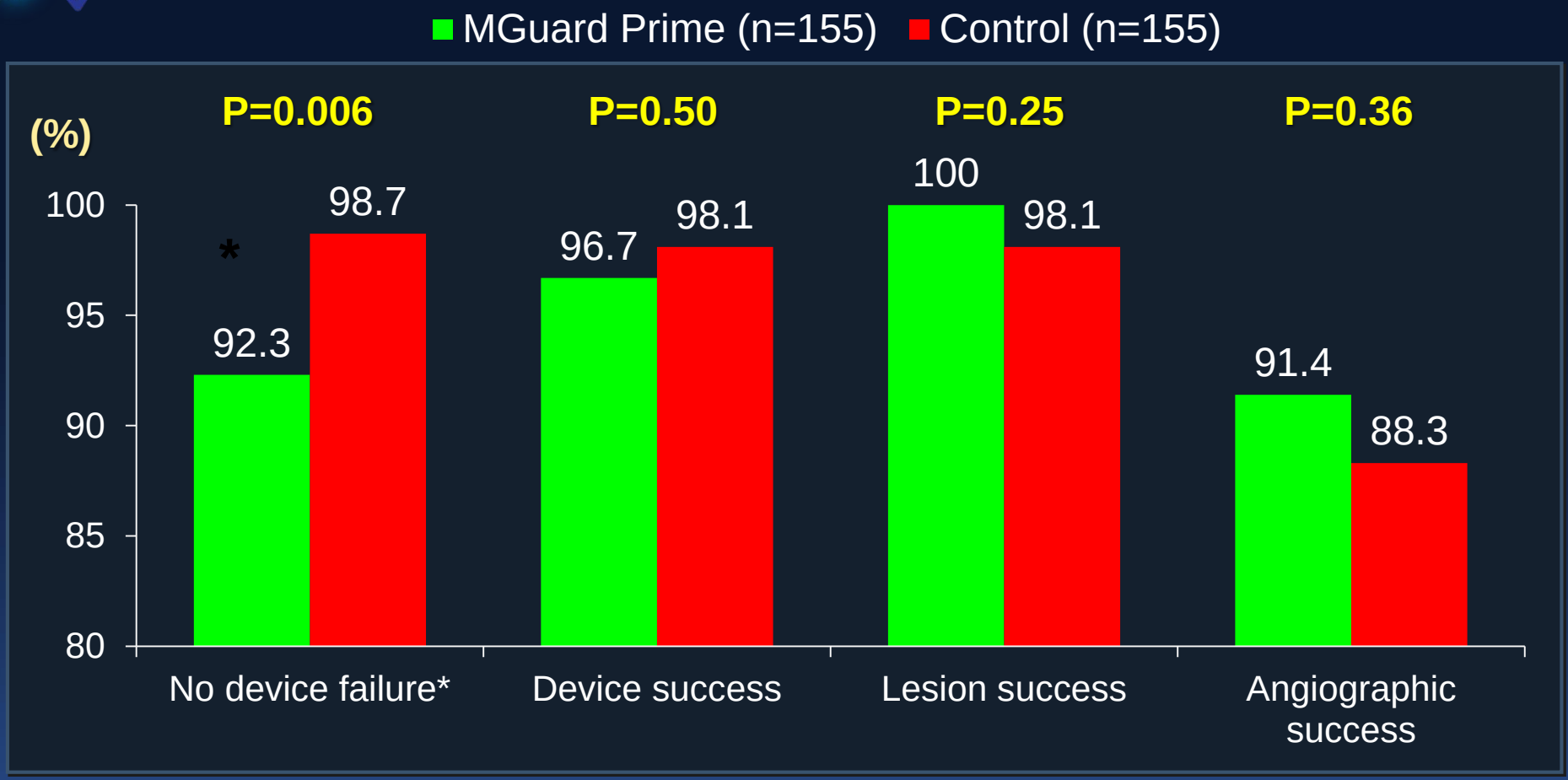
MASTER II Procedural Medications

	MGuard Prime (n=155)	Control stent (n=155)	*P* value
Anticoagulation, peri-procedural			
– Unfractionated heparin	70.1%	67.8%	0.65
– Glycoprotein IIb/IIIa inhibitor	45.5%	53.3%	0.17
– Bivalirudin	37.0%	31.6%	0.32
Anti-platelet agents, discharge			
– Aspirin	98.7%	96.7%	0.28
– ADP antagonists	98.7%	98.0%	0.68
– Clopidogrel	44.8%	45.4%	0.92
– Prasugrel	29.2%	31.6%	0.65
– Ticagrelor	33.1%	33.6%	0.94

MASTER II Procedures

	MGuard Prime (n=155)	Control stent (n=155)	*P* value
Aspiration performed	60.6%	62.6%	0.73
Balloon pre-dilatation performed	49.7%	34.8%	0.008
Direct stenting	13.5%	18.1%	0.28
≥1 stent implanted	99.4%	99.4%	1.00
≥2 stents implanted	9.7%	14.2%	0.22
Stent type			
– MGuard Prime	96.8%	0%	<0.0001
– Bare metal stent	3.9%	20.1%	<0.0001
– Drug-eluting stent	3.2%	80.5%	<0.0001
Total stent length, mm	18 [18, 23]	23 [18, 28]	0.08
Post stent dilatation performed	37.4%	33.8%	0.50
Maximal device size, mm	3.5 [3.0, 4.0]	3.5 [3.0, 3.5]	0.38
Maximal dilatation pressure, atm	16 [14, 18]	16 [14, 18]	0.12

MASTER II **Device Success**



Device success: <50% final residual stenosis using only the randomized stent
Lesion success: <50% final residual stenosis using any percutaneous method
Angiographic success: <50% final residual stenosis and final TIMI 3 flow

*MGuard Prime arm: failure to cross lesion (4 [2.6%]); stent dislodgement (5 [3.2]%); failure to deploy or deployment at unintended site (5 [3.2]%). Control arm: failure to cross lesion (1 [0.6%]); other (1 [0.6%])

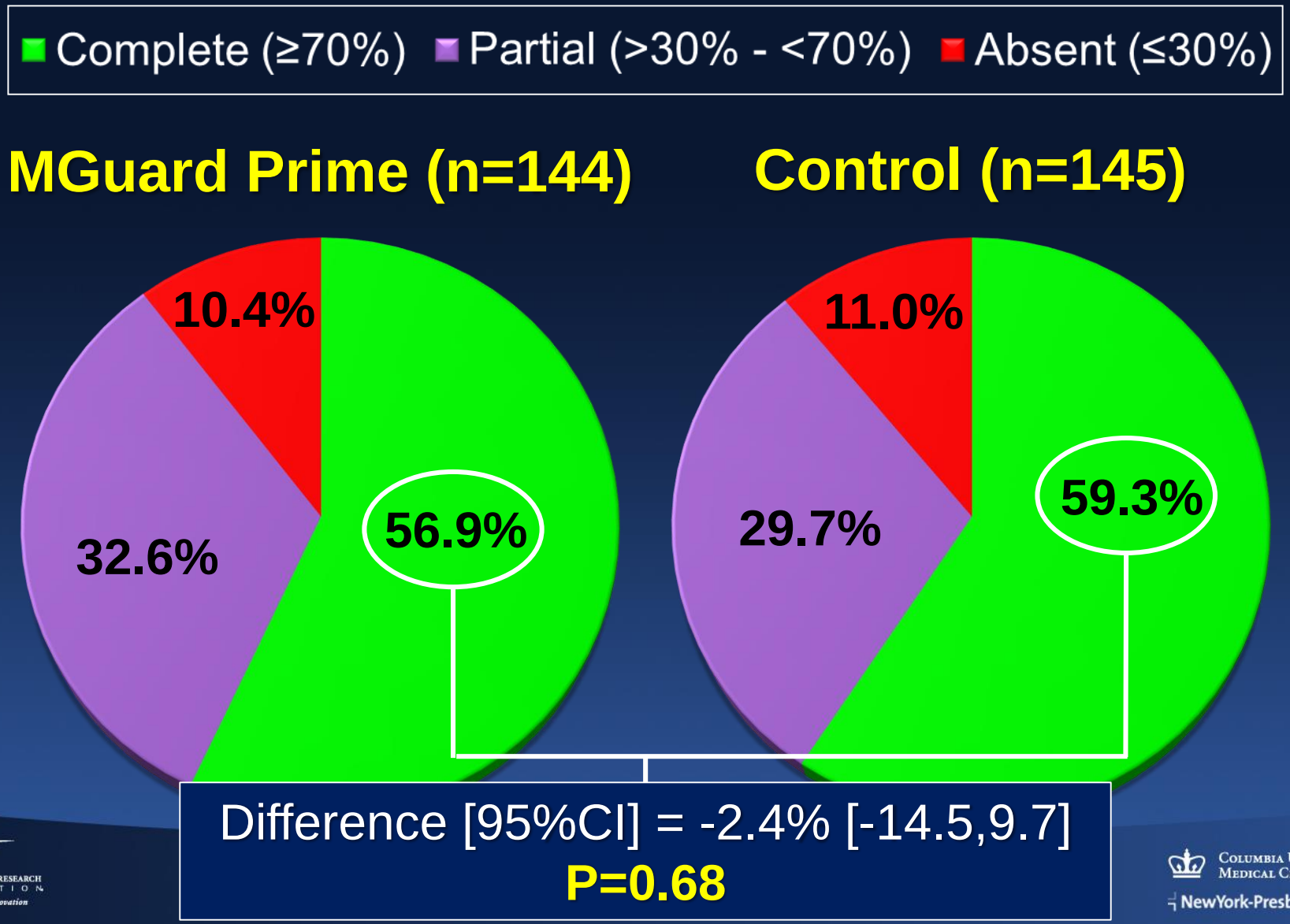
MASTER II Procedural Results

	MGuard Prime (n=152)	Control stent (n=155)	*P* value
TIMI flow = 3	91.4%	89.0%	0.46
TIMI flow = 2	7.9%	9.1%	0.71
TIMI flow = 0/1	0.7%	1.9%	0.62
Corrected TIMI frame count	19.5 [14.0, 24.0]	18.0 [14.0, 24.0]	0.47
IPTE*	11.2%	11.6%	0.91
RVD, mm	3.07 [2.77, 3.37]	3.05 [2.72, 3.37]	0.54
MLD, in-stent, mm	2.80 [2.54, 3.10]	2.87 [2.52, 3.12]	0.96
MLD in-lesion, mm	2.57 [2.21, 2.83]	2.53 [2.14, 2.77]	0.26
DS%, in-stent	7.7 [2.7, 12.6]	7.0 [2.4, 13.0]	0.82
DS%, in-lesion	16.1 [10.1, 24.0]	16.9 [11.1, 24.8]	0.32

*IPTE = intraprocedural thrombotic events

MASTER II Primary Endpoint

Complete ST-segment resolution



MASTER II 30-day Clinical Events

	MGuard Prime (n=155)	Control stent (n=155)	*P* value
MACE	4 (2.6%)	7 (4.5%)	0.36
– Cardiac mortality	1 (0.6%)	3 (1.9%)	0.62
– Reinfarction	2 (1.3%)	2 (1.3%)	1.00
– TLR, ischemia-driven	4 (2.6%)	4 (2.6%)	1.00
Death, all-cause	1 (0.6%)	3 (1.9%)	0.62
TVR, ischemia-driven	4 (2.6%)	4 (2.6%)	1.00
Stent thrombosis, def/prob	4 (2.6%)	5 (3.2%)	1.00
– Definite	4 (2.6%)	4 (2.6%)	1.00
– Probable	0 (0%)	1 (0.6%)	1.00
BARC bleeding, 2-5	1 (0.5%)	2 (1.3%)	1.00

MASTER II 3-5 Day MRI Substudy

	MGuard Prime (n=28)	Control stent (n=29)	*P* value
Total LV myocardial mass, gms	129.5 [107.0, 154.5]	122.0 [112.0, 136.0]	0.57
Infarct mass, grams	31.4 [14.9, 50.5]	35.8 [16.4, 57.1]	0.45
Infarct mass (% total LV mass)	23.6 [14.2, 30.1]	29.3 [14.3, 43.0]	0.16
Total MVO, grams	0.3 [0.0, 1.8]	0.5 [0.0, 6.7]	0.39
MVO (% total LV mass)	0.2 [0.0, 1.1]	0.4 [0.0, 4.8]	0.29
Abnormal wall motion score	27 [24, 28]	26 [23, 27]	0.27
LVEF (%)	44.5 [33.8, 47.9]	43.9 [40.2, 50.1]	0.29

LV = left ventricular; EF = ejection fraction; MVO = microvascular obstruction

MASTER II
Limitations

- Single-blind
- Most control pts received DES → substantial difference between MGuard Prime and control arm in restenosis anticipated → trial terminated
- Early termination → underpowered for all endpoints

MASTER I + II Pooled Analysis

- 743 randomized pts -

	MASTER I	MASTER II
Number of patients	433	310
- MRI substudy	59	57
Number of sites	50	46
Control arm: DES	39.8%	80.5%
MGuard arm: % Prime	12.0%	100%
Prasugrel/ticagrelor at d/c	30.1%	63.7%
Bivalirudin	11.8%	34.3%
GP IIb/IIIa inhibitor	83.1%	49.3%
Symptoms to device, mins	220 [147, 333]	171 [125, 292]
Infarct artery = LAD	40.2%	37.1%
Baseline RVD, mm	3.11 [2.87, 3.40]	3.02 [2.71, 3.33]
Baseline TIMI 0/1	70.2%	69.7%
Aspiration	66.5%	61.6%

MASTER I + II Procedural Results

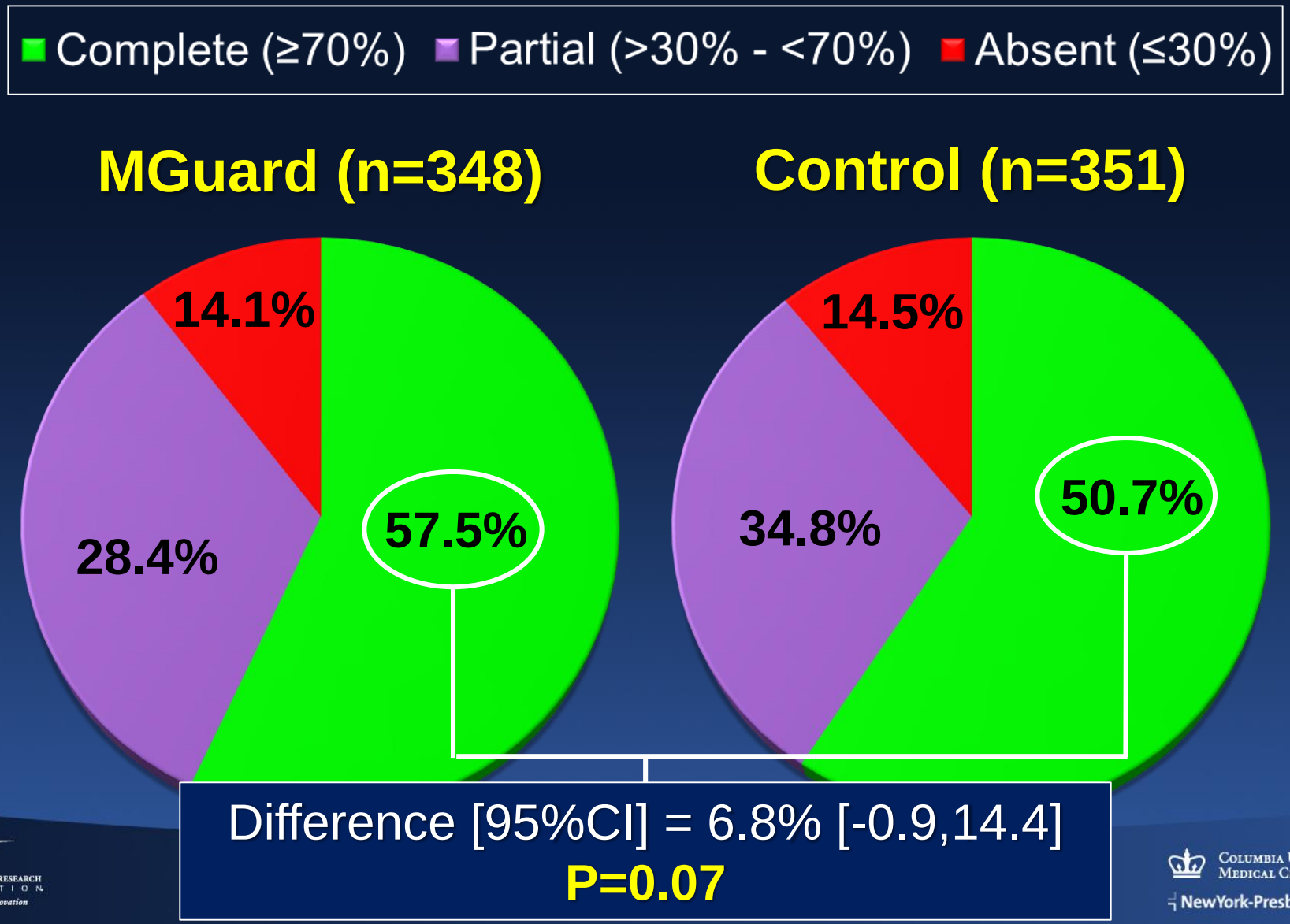
	MGuard (n=372)	Control stent (n=371)	*P* value
Any device failure	5.6%	1.3%	0.03
Device success	96.2%	98.7%	0.04
Lesion success	100%	98.9%	0.62
Angiographic success	91.6%	84.9%	0.005
TIMI flow = 3	91.6%	85.4%	0.008
TIMI flow = 2	7.0%	10.5%	0.09
TIMI flow = 0/1	1.4%	4.1%	0.02
Corrected TIMI frame count	18.0 [13.0, 24.0]	18.0 [14.0, 22.0]	0.63
IPTE*	17.1%	19.7%	0.36

Device success: <50% final residual stenosis using only the randomized stent
Lesion success: <50% final residual stenosis using any percutaneous method
Angiographic success: <50% final residual stenosis and final TIMI 3 flow

*IPTE = intraprocedural thrombotic events

MASTER I + II

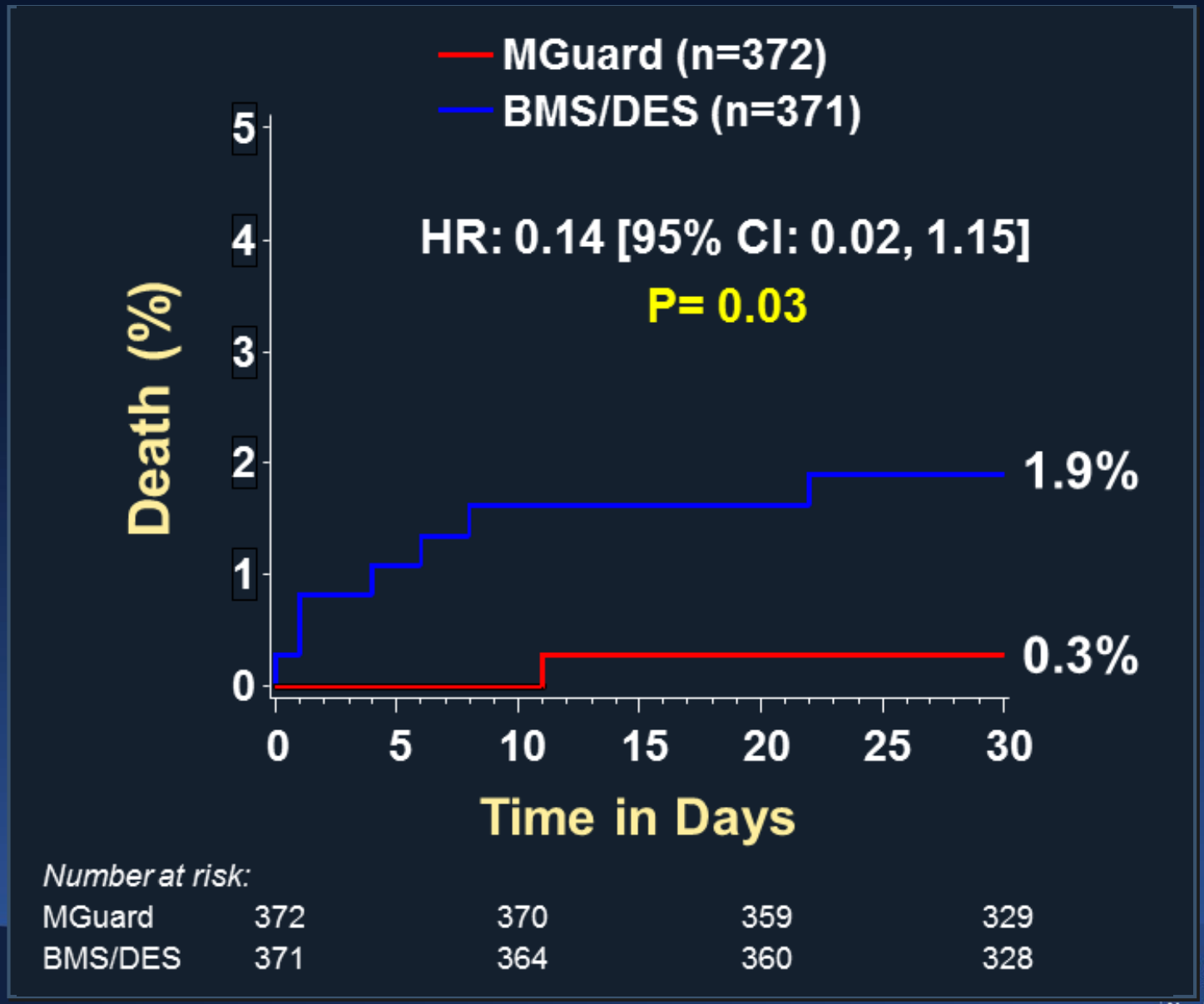
Complete ST-segment resolution



MASTER I + II 30-day Clinical Events

	MGuard (n=372)	Control stent (n=371)	*P* value
MACE	8 (2.2%)	12 (3.2%)	0.36
– Cardiac mortality	1 (0.3%)	7 (1.9%)	0.04
– Reinfarction	5 (1.3%)	4 (1.1%)	1.00
– TLR, ischemia-driven	8 (2.2%)	5 (1.3%)	0.40
Death, all-cause	1 (0.3%)	7 (1.9%)	0.04
TVR, ischemia-driven	9 (2.4%)	5 (1.3%)	0.28
Stent thrombosis, def/prob	7 (1.9%)	7 (1.9%)	1.00
– Definite	7 (1.9%)	5 (1.3%)	0.56
– Probable	0 (0%)	2 (0.5%)	0.25
TIMI major/minor bleeding	7 (1.9%)	8 (2.2%)	0.79

MASTER I + II 30-day Mortality



MASTER I + II 3-5 Day MRI Substudy

	MGuard (n=58)	Control stent (n=58)	*P* value
Total LV myocardial mass, gms	135.5 [112.0, 158.0]	130.0 [117.0, 156.0]	0.57
Infarct mass, grams	21.9 [12.5, 40.0]	29.0 [16.0, 48.7]	0.22
Infarct mass (% total LV mass)	20.5 [8.9, 28.1]	21.5 [12.0, 30.1]	0.26
Total MVO, grams	0.3 [0.0, 1.7]	1.0 [0.0, 3.8]	0.08
MVO (% total LV mass)	0.3 [0.0, 1.2]	0.8 [0.00, 2.5]	0.14
Abnormal wall motion score	26 [21, 27]	25 [21, 27]	0.83
LVEF (%)	46.9 [39.2, 50.0]	45.2 [40.9, 52.6]	0.60

LV = left ventricular; EF = ejection fraction; MVO = microvascular obstruction

MASTER II **Conclusions**

- The MASTER II trial was terminated prematurely due to the control arm shift in physician preference from BMS to DES, accelerating the plans to create a drug-eluting MGuard
- The significant differences in complete ST-segment resolution and TIMI-3 flow present in MASTER I with the MGuard were not apparent in MASTER II, most likely due to better outcomes in the control arm in MASTER II
- Differences in sites, patient characteristics, technique and pharmacotherapy between MASTER I and II may have contributed to these differences, as well as play of chance given the modest sample size

MASTER I and MASTER II
Conclusions

- The pooled data from 743 randomized pts in the MASTER I and MASTER II trials suggest that compared to control stents, the MGuard may be associated with improved reperfusion success and reduced 30-day mortality
- An adequately powered randomized trial is warranted to determine whether the MGuard embolic protection stent improves outcomes in pts with STEMI undergoing primary PCI